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

NCT Number: NCT06263478

Document Date: Protocol INCA 34176-358 Am 2 Version 3 30 JAN 2026

Clinical Study Protocol

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

Product:	**Axatilimab (INCA034176)**
Phase of Study:	**3**
Sponsor:	**Incyte Biosciences Japan G.K.** **Tokyo Midtown Hibiya 12F** **1-1-2 Yurakucho Chiyoda-ku, Tokyo 100-0006**
Original Protocol:	**20 DEC 2023**
Amendment 1:	**15 NOV 2024**
Amendment 2:	**30 JAN 2026**

This study will be performed in accordance with ethical principles as per the updated Declaration of Helsinki (Finland 2024) and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations, including WMO (Medical Research Involving Human Participants Act) and Clinical Trials Regulation (EU) No. 536/2014, in which the study is being conducted.

The information in this document is confidential. No part of this information may be duplicated, referenced, or transmitted in any form or by any means (electronic, mechanical, photocopy, recording, or otherwise) without prior written consent.

INVESTIGATOR'S AGREEMENT

I have read the INCA 34176-358 Protocol Amendment 2 (dated 30 JAN 2026) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

TABLE OF CONTENTS

TITLE PAGE 1
INVESTIGATOR'S AGREEMENT 2
TABLE OF CONTENTS 3
LIST OF ABBREVIATIONS 9
1. PROTOCOL SUMMARY 12
2. INTRODUCTION 19
2.1. Background 19
2.2. Study Rationale 20
2.2.1. Scientific Rationale for Study Design 21
2.2.2. Justification for Dose 21
2.2.3. Brief Epidemiology of Disease Studied and Minority Populations 22
2.3. Benefit/Risk Assessment 22
3. OBJECTIVES AND ENDPOINTS 24
4. STUDY DESIGN 25
4.1. Overall Design 25
4.2. Overall Study Duration 26
4.3. Study Termination 26
5. STUDY POPULATION 27
5.1. Inclusion Criteria 27
5.2. Exclusion Criteria 29
5.3. Lifestyle Considerations 30
5.4. Screen Failures 30
5.5. Recruitment Strategy and Retention of Participants 30
5.6. Replacement of Participants 30
6. STUDY TREATMENT 31
6.1. Study Treatment Administered 31
6.2. Preparation, Handling, and Accountability 31
6.3. Measures to Minimize Bias: Randomization and Blinding 32
6.4. Study Treatment Compliance 32
6.5. Stopping Rules and Dose Modifications 33
6.5.1. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug 33

6.5.1.1. Elevation of AST, ALT, Bilirubin, CPK, Amylase, or Lipase 34
6.5.1.2. Other Nonhematologic Toxicities....35
6.5.1.3. Hematologic Toxicities: Dose Modification Guidelines for Axatilimab 35
6.5.1.4. Infusion-Related Reaction 35
6.5.1.5. Change to Dose Schedule for Axatilimab 36
6.5.2. Criteria for Permanent Discontinuation of Study Drug 37
6.5.3. Discontinuation of Study Drug for Lack of Efficacy 37
6.6. Concomitant Medications and Procedures 37
6.6.1. Permitted Medications and Procedures 37
6.6.1.1. Corticosteroids 38
6.6.1.2. Calcineurin Inhibitors and Mycophenolate Mofetil 38
6.6.2. Restricted Medications and Procedures 39
6.6.3. Prohibited Medications and Procedures 39
6.7. Continued Access to Study Drug After the End of the Study 40
7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL 40
7.1. Discontinuation of Study Treatment 40
7.1.1. Reasons for Discontinuation 40
7.1.2. Discontinuation Procedures 41
7.2. Participant Withdrawal From the Study 41
7.3. Lost to Follow-Up 41
8. STUDY ASSESSMENTS AND PROCEDURES 42
8.1. Administrative and General Procedures 42
8.1.1. Informed Consent Process 42
8.1.2. Legal Guardian Consent and Pediatric Participant Assent Processes 43
8.1.3. Screening Procedures 44
8.1.4. Interactive Response Technology Procedure 44
8.1.5. Distribution of Study Participation Card 44
8.1.6. Demography and Medical History 44
8.1.6.1. Demographics and General Medical History 44
8.1.6.2. Disease Characteristics and Treatment History 45
8.1.7. Chronic GVHD Diagnosis and Staging at Screening 45
8.2. Efficacy Assessments 45

8.2.1. Response Determination According to 2014 NIH Consensus Definitions....45
8.2.2. Response Determination for Pediatric Participants....46
8.2.3. Physician-Reported Global and Organ-Specific cGVHD Activity Assessments....46
8.2.4. Participant-Reported cGVHD Activity Assessment (mLSS)....47
8.2.5. Medical Resource Utilization and Health Economics....47
8.3. Safety Assessments....47
8.3.1. Adverse Events....47
8.3.2. Physical Examinations....48
8.3.3. Vital Signs....48
8.3.4. Neurological Examination....49
8.3.5. Karnofsky/Lansky Performance Status....49
8.3.6. Electrocardiograms....50
8.3.7. Laboratory Assessments....50
8.3.8. Bone Turnover Markers....50
8.3.9. Bone Density DEXA Scan....51
8.3.10. Pulmonary Function Tests....51
8.3.11. Pregnancy Testing....51
8.3.12. Serology....51
8.3.12.1. Hepatitis Screening....51
8.3.12.2. HIV Screening....52
8.3.12.3. Tuberculosis Screening....52
8.3.13. Chimerism and Graft Failure....52
8.4. Pharmacokinetic Assessments....52
8.4.1. Blood Sample Collection....52
8.4.2. Immunogenicity Assessments....53
8.5. Pharmacodynamic and Translational Assessments....53
8.5.1. Whole Blood PBMC for Pharmacodynamic Assessments....54
8.5.2. Serum for Biomarker Assessments....54
8.6. Storage and Future Use of Biological Samples....54
8.7. Unscheduled Visits....54
8.8. End of Treatment....55
8.9. Follow-Up....55

8.9.1. Safety Follow-Up....55
8.9.2. Post-Treatment Disease Follow-Up....55
9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING....56
9.1. Definition of Adverse Event....56
9.2. Definition of Serious Adverse Event....57
9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events....58
9.4. Reporting of Serious Adverse Events....60
9.5. Potential Drug-Induced Liver Injury....62
9.6. Events of Clinical Interest....62
9.6.1. Adverse Events of Special Interest....62
9.7. Emergency Unblinding of Treatment Assignment....62
9.8. Pregnancy....62
9.9. Warnings and Precautions....63
9.10. Product Complaints....63
9.11. Treatment of Overdose....63
10. STATISTICS....64
10.1. Sample Size Determination....64
10.2. Populations for Analysis....64
10.3. Level of Significance....65
10.4. Statistical Analyses....65
10.4.1. Primary Analysis....65
10.4.2. Secondary Analysis....65
10.4.2.1. Pharmacokinetics....66
10.4.2.2. Antidrug Antibody Immunogenicity....66
10.4.3. Safety Analyses....66
10.4.3.1. Adverse Events....66
10.4.3.2. Clinical Laboratory Tests....66
10.4.3.3. Vital Signs....67
10.4.3.4. Electrocardiograms....67
[redacted]
10.5. Interim Analysis....67

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS....68
11.1. Investigator Responsibilities....68
11.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP....69
11.1.2. Identification of the Coordinating Principal Investigator....70
11.2. Data Management....70
11.3. Data Quality Assurance....72
11.4. Data Privacy and Confidentiality of Study Records....72
11.5. Financial Disclosure....73
11.6. Publication Policy....73
11.7. Study and Site Closure....74
12. REFERENCES....75
APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS....77
APPENDIX B. REQUIRED LABORATORY ANALYTES....78
APPENDIX C. STAGING OF CHRONIC GVHD (NIH CRITERIA)....79
APPENDIX D. ORGAN-SPECIFIC SEVERITY SCORING....80
APPENDIX E. GLOBAL CHRONIC GVHD ACTIVITY ASSESSMENT (CLINICIAN REPORT)....83
APPENDIX F. CHRONIC GVHD MODIFIED LEE SYMPTOM SCALE....87
APPENDIX G. DISEASE RISK INDEX....88
APPENDIX H. MANAGEMENT OF POTENTIAL HY'S LAW CASES/POTENTIAL DILI....90
APPENDIX I. PROTOCOL AMENDMENT SUMMARY OF CHANGES....94

LIST OF TABLES

Table 1: Primary Objective and Endpoint....12
Table 2: Main Study Design Elements....12
Table 3: Schedule of Activities....14
Table 4: Schedule of Laboratory Assessments....17
Table 5: Objectives and Endpoints....24
Table 6: Study Treatment Information....31
Table 7: Dose-Reduction Levels for Axatilimab....33
Table 8: Dose Modification Guidelines for Axatilimab Based on Laboratory Results....34

Table 9: Other Nonhematologic Toxicities: Dose Modification Guidelines for Axatilimab 35
Table 10: Hematologic Toxicities: Dose Modification Guidelines for Axatilimab 35
Table 11: Guidance for Treatment of Infusion-Related Reactions 36
Table 12: Response Determination for Chronic GVHD Based on Clinical Assessment 46
Table 13: Karnofsky/Lansky Performance Status Scale 49
Table 14: Pharmacokinetic and Antidrug Antibody Blood Sample Timing 53
Table 15: Biomarker/Translational Sample Timing 54
Table 16: Populations for Analysis 65

LIST OF FIGURES

Figure 1: Study Design Schema 13

LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
ADA	antidrug antibody
AE	adverse event
aGVHD	acute graft-versus-host disease
allo-HSCT	allogeneic hematopoietic stem cell transplantation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BAP	bone-specific alkaline phosphatase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CD	cluster of differentiation
cGVHD	chronic graft-versus-host disease
CI	confidence interval
CNI	calcineurin inhibitor
CPK	creatine phosphokinase
CR	complete response
CSF-1	colony-stimulating factor 1
CSF-1R	colony-stimulating factor 1 receptor
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTX	carboxy-terminal collagen crosslinks
DEXA	dual-energy x-ray absorptiometry
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration

Abbreviations and Special Terms	Definition
FEV	forced expiratory volume
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GVHD	graft-versus-host disease
HBcAb	hepatitis core antibody
HBcAg	hepatitis core antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HRT	hormone-replacement therapy
HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
JDCHCT	Japanese Data Center for Hematopoietic Cell Transplantation
JSH	Japan Society of Hepatology
JSTCT	Japanese Society for Transplantation and Cellular Therapy

Abbreviations and Special Terms	Definition
LDL	low-density lipoprotein
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mLSS	modified Lee symptom scale
MMF	mycophenolate mofetil
NCI	National Cancer Institute
NIH	National Institutes of Health
NK	natural killer
OMRS	Oral Mucosa Rating Scale
ORR	overall response rate
PBMC	peripheral blood mononuclear cell
PFT	pulmonary function test
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
P-ROM	photographic range of motion
PT	prothrombin time
QxW	once every x weeks
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SoA	schedule of activities
SOP	standard operating procedure
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

Protocol Full 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

Short 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

Protocol Number: INCA 34176-358

Objectives and Endpoints:

Table 1 presents the primary objective and endpoint.

Table 1: Primary Objective and Endpoint

Objective	Endpoint
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.

Overall Design:

Table 2 presents the main study design elements. Further study details are presented after the table.

Table 2: Main Study Design Elements

Study Phase	Phase 3
Clinical Indication	Treatment of patients with recurrent or refractory active cGVHD who have received at least 2 prior lines of systemic therapy.
Population	Participants at least 6 years of age 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.
Number of Participants	Approximately 20 participants will be enrolled in this study.
Study Design	This is a Phase 3, open-label, multicenter study to evaluate the efficacy and safety of axatilimab 0.3 mg/kg Q2W IV in Japanese participants with recurrent or refractory active cGVHD.

Table 2: Main Study Design Elements (Continued)

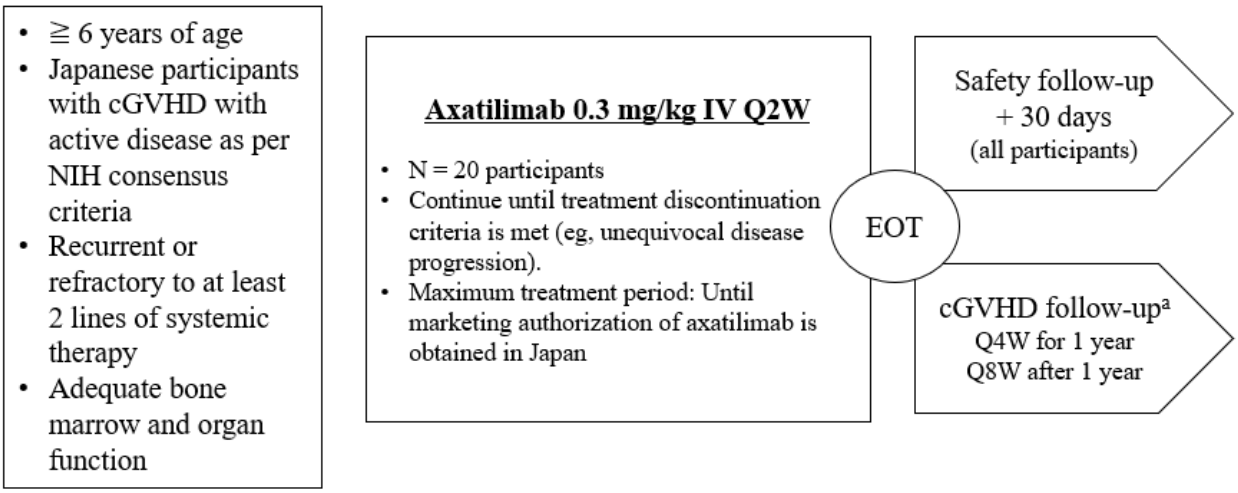
Estimated Duration of Study Participation	Participation will include up to 28 days for screening, continuous treatment in consecutive 28-day cycles until unequivocal disease progression or unacceptable toxicity, and 30 (+ 7) days for safety follow-up. It is estimated that an individual will participate for approximately 8 to 10 months. Participants who, in the opinion of the investigator, are deriving individual clinical benefit may continue treatment with axatilimab for a maximum duration up to the time of marketing authorization in Japan.
Data Monitoring Committee	No

Treatment Groups and Duration:

Approximately 20 Japanese participants with recurrent or refractory active cGVHD eligible for enrollment will be entered the study. Participants will be administered axatilimab 0.3 mg/kg Q2W IV for a maximum duration up to the time of marketing authorization in Japan. The end of the study will occur once the last required assessment is completed and the study is closed.

The study design schema is shown in Figure 1, and the SoA is shown in Table 3. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema



[a] Only participants who achieve CR or PR and discontinue axatilimab for reasons other than disease progression.

Table 3: Schedule of Activities

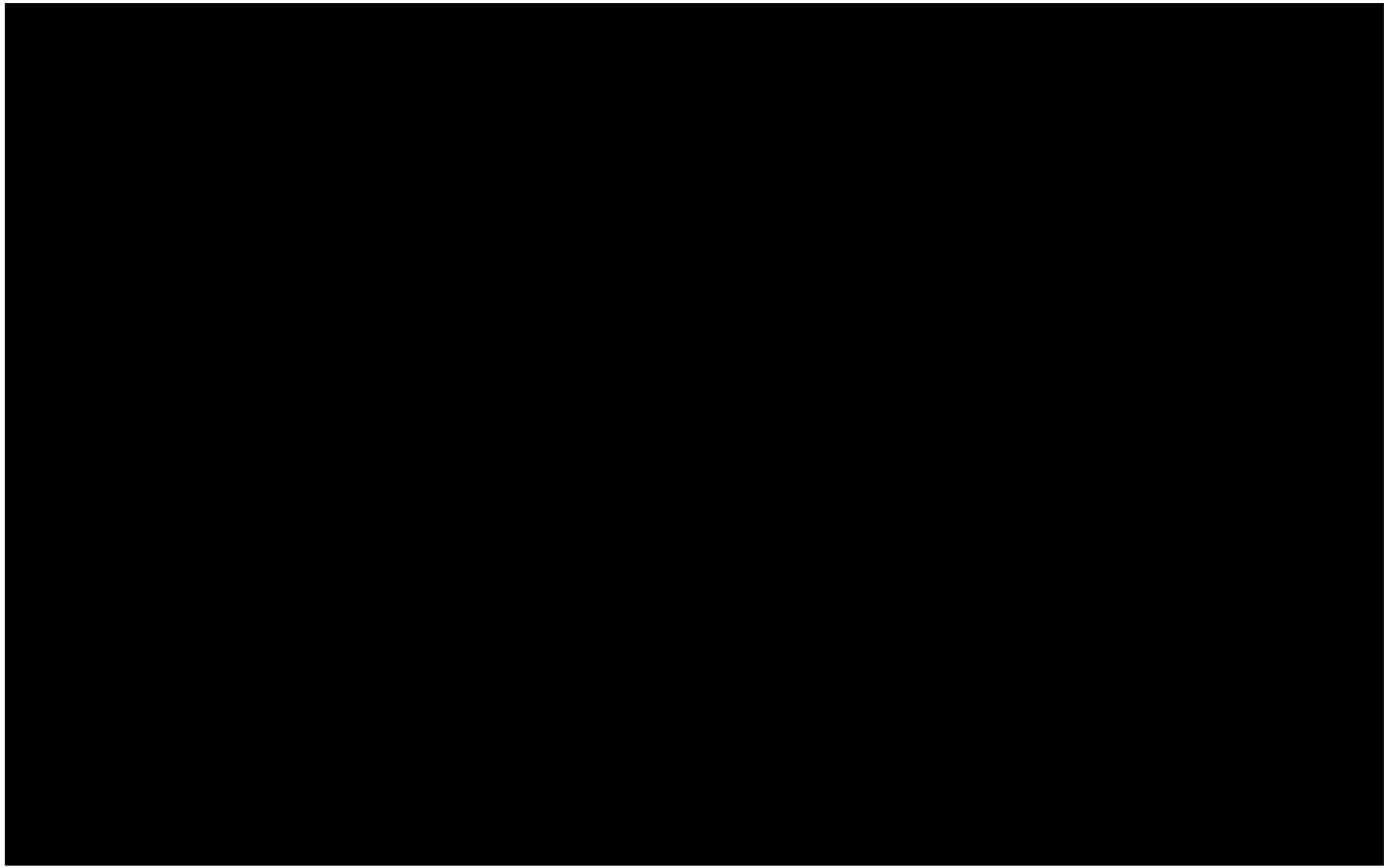


Table 3: Schedule of Activities (Continued)

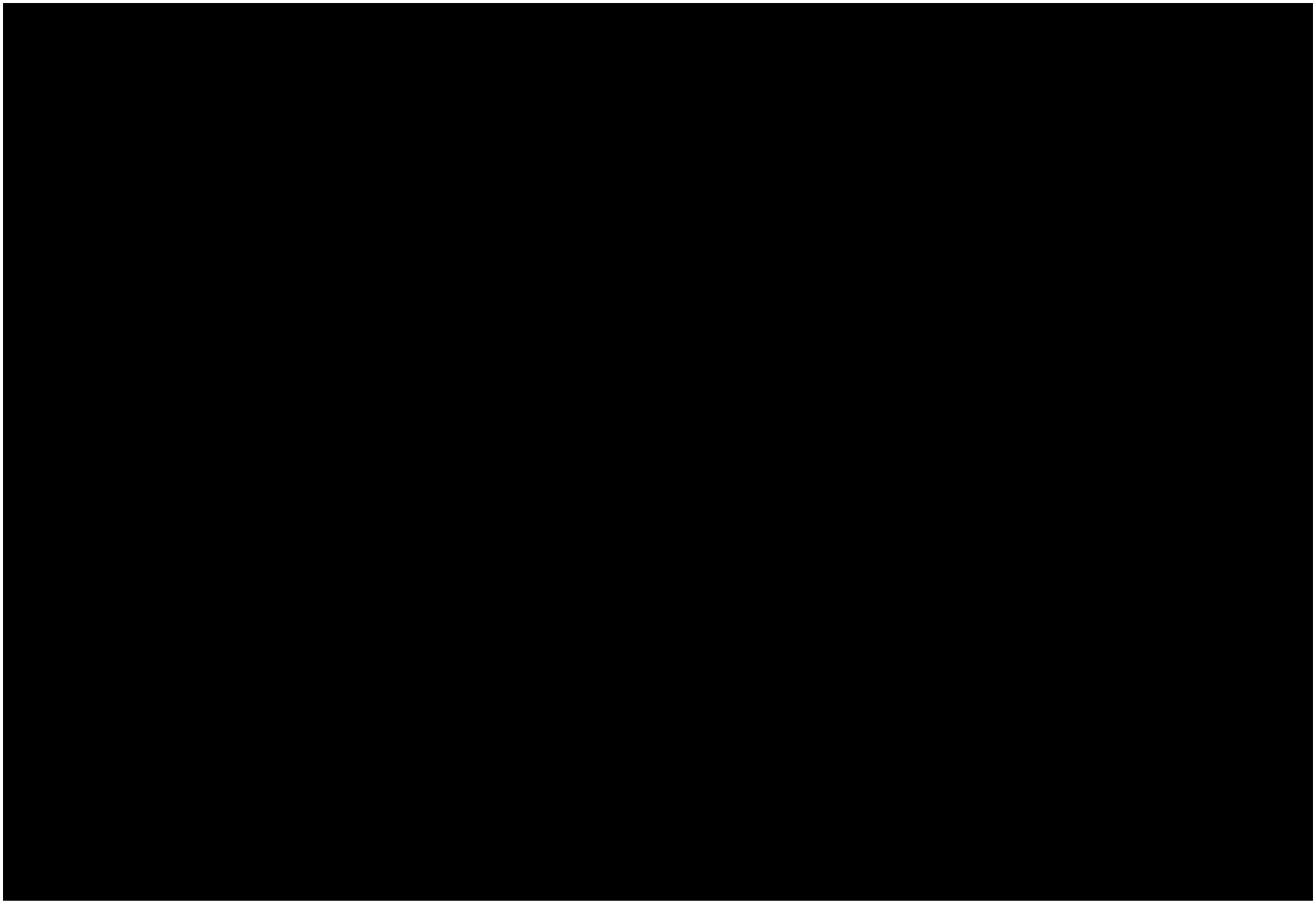


Table 3: Schedule of Activities (Continued)



Table 4: Schedule of Laboratory Assessments



Table 4: Schedule of Laboratory Assessments (Continued)



2. INTRODUCTION

2.1. Background

Allogeneic hematopoietic stem cell transplantation is a curative immunotherapy for patients with blood-related malignancies including leukemia, lymphoma, and myeloma. Additionally, allo-HSCT provides normal hematopoietic function in patients with nonmalignant hematologic disorders including severe aplastic anemia, inherited metabolic disorders, and hemoglobinopathies (Copelan 2006). Graft-versus-host disease is a major limitation to the success of allo-HSCT and occurs when donor-derived immune cells in a bone-marrow or stem-cell graft recognize the transplant recipient as foreign, thereby initiating an adverse immune reaction leading to an inflammatory cascade with resultant tissue damage, organ failure, or even death. Chronic GVHD has been historically characterized by autoimmune and alloimmune dysregulation occurring after the first 100 days of allo-HSCT, with the median onset of cGVHD approximately 6 months after allo-HSCT (Baird et al 2010). Risk factors for cGVHD include prior aGVHD, grafting with growth-factor mobilized blood cells, the use of female donors for male recipients, and the use of unrelated donors (Flowers et al 2011).

Approximately 32,000 allo-HSCT procedures are performed annually worldwide (Niederwieser et al 2016) with up to 60% of patients receiving human leucocyte antigen–identical marrow grafts, and 70% of patients who survive past 100 days after receiving alternative donor marrow grafts develop cGVHD (Lee et al 2003). Additionally, the prevalence and severity of cGVHD, occurring in 30% to 70% of patients with allo-HSCT (Lee and Flowers 2008), has increased over the past 2 decades. This increase may be attributable to several factors including the following: the increased use of mobilized peripheral blood stem cell grafts (containing higher numbers of donor T cells than bone marrow; the age of recipients rising from 55 to 75 years due to development of better tolerated, reduced intensity conditioning; and improvements in survival during the first months after allo-HSCT.

Chronic GVHD has a wide range of pleomorphic manifestations, and various complications can emerge from both the disease and its treatment. It is a chronic illness that can have devastating effects on quality of life. Clinical manifestations can impair activities of daily living and often last for years. Manifestations of cGVHD can resemble autoimmune or other immune-mediated disorders such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency. Chronic GVHD generally involves several organs or anatomical sites; patients frequently have erythematous rash, enteritis, or hepatic involvement characterized by transaminase elevation or hyperbilirubinemia at initial presentation and intermittently during the course of the disease. Manifestations typically appear within the first year after HSCT, most often when doses of immunosuppressive medications are weaned. The disease can begin as early as 2 months and as late as 7 years after HSCT, although onset at more than 1 year from HSCT occurs in < 10% of cases (Flowers and Martin 2015).

With the widespread use of unrelated transplantation in Japan, the total number of patients undergoing transplantation is increasing, and approximately 3900 allo-HSCTs were performed in 2020 (JDCHCT 2023). In addition, unrelated peripheral blood stem cell transplantation was introduced in 2021, and the number of cases has been gradually increasing.

Although Japanese patients compared with White patients have a lower incidence of cGVHD (bone marrow transplantation, 15% vs 30% [p = 0.002]; peripheral blood stem cell transplantation, 37% vs 45% [p < 0.001]), with more frequent cGVHD of the mouth, eyes, and liver and less frequent GI cGVHD, when the condition requires systemic treatment, the extent of organ invasion and the duration of immunosuppressive treatment are not significantly different between races (Inamoto et al 2019). Thus, cGVHD also presents an unmet medical need in Japanese patients.

2.2. Study Rationale

While the pathophysiological understanding of cGVHD is emerging and there have been recent advances in second-line treatment of the disease, there remains a long-standing reliance on corticosteroids as the mainstay of front-line treatment. Steroid administration can relieve symptoms and delay disease progression; however, this approach is associated with significant toxicity and emergence of resistance (Flowers and Martin 2015, MacDonald et al 2017). An effort to decrease corticosteroid doses has led to their use in combination with other immunosuppressants, such as cyclosporine, tacrolimus, and sirolimus, in front-line or second-line settings despite a lack of clinical evidence supporting additional efficacy after combining these agents with corticosteroids (Miklos et al 2017).

Approximately 50% to 60% of patients with cGVHD require secondary treatment within 2 years after initial systemic treatment. In 2017 Imbruvica® (ibrutinib), a Bruton tyrosine kinase inhibitor, became the first FDA-approved therapy for the treatment of adult patients with cGVHD, indicated for patients who have received at least 1 line of systemic therapy (Imbruvica 2023). The side effects of ibrutinib are significant, with 33% of participants discontinuing treatment due to an AE and 31% of participants requiring a dose reduction in the pivotal evaluation of ibrutinib in participants with cGVHD (Miklos et al 2017).

In Japan, the regulatory endorsement of extracorporeal photopheresis was conferred for the indication of steroid-resistant or intolerant cGVHD in DEC 2020. Subsequently, ibrutinib received approval for employment in cases of cGVHD after HSCT (in instances of inadequate response to steroids) in SEP 2021, entailing its inclusion in the roster of drugs covered by the national health insurance. More recently, the Janus kinase inhibitor, ruxolitinib, garnered approval for the treatment of steroid-refractory cGVHD within the Japanese jurisdiction.

While these therapeutic modalities demonstrate clinical efficacy in managing steroid-refractory cGVHD, persisting challenges are encountered, encompassing a subset of nonresponsive cases and the advent of treatment-related toxicities necessitating temporary cessation or discontinuation. Presently, there exists no standardized treatment for patients with cGVHD who exhibit suboptimal responses to second-line systemic therapies, which necessitates the need for innovative interventions.

Axatilimab is a humanized immunoglobulin G4 mAb with high affinity against CSF-1R. Axatilimab can affect the migration, proliferation, differentiation, and survival of circulating monocyte populations and monocyte-derived macrophages by binding to CSF-1R and blocking activation by its 2 known ligands, CSF-1 and IL-34.

Blocking CSF-1R signaling with axatilimab is expected to reduce the circulating levels of pathogenic monocyte-derived macrophage precursors and inhibit their activation in tissues, thereby providing an opportunity to therapeutically intervene in diseases such as cGVHD (Alexander et al 2014).

The clinical efficacy of axatilimab was confirmed by Study SNDX-6352-0504 (AGAVE-201), which recently completed primary analysis. The study was designed to evaluate axatilimab monotherapy at 3 dose levels (0.3 mg/kg Q2W, 1.0 mg/kg Q2W, and 3.0 mg/kg Q4W IV) in participants with cGVHD who had received 2 or more lines of prior therapy. The AGAVE-201 study met its primary endpoint for all doses, with the most favorable benefit:risk profile observed at the 0.3 mg/kg Q2W dose. Treatment with axatilimab 0.3 mg/kg Q2W (N = 80) resulted in the highest ORR in the first 6 cycles (74%; 95% CI: 62.7, 83.0) and had a manageable safety profile.

Current clinical data support the evaluation of axatilimab in Japanese participants with recurrent or refractory cGVHD to potentially address unmet medical needs in this indication.

2.2.1. Scientific Rationale for Study Design

This study is designed to confirm the efficacy and safety of axatilimab 0.3 mg/kg Q2W IV in Japanese participants with recurrent or refractory cGVHD who have received at least 2 lines of systemic therapy.

There is no standard treatment recommended for recurrent or refractory cGVHD after at least 2 lines of therapy according to JSTCT guidelines. In view of the current situation, in which third-line or subsequent treatment is selected from recently approved drugs for steroid-dependent or steroid-refractory cGVHD (eg, ibrutinib, extracorporeal photopheresis, and ruxolitinib), it is not appropriate to set a valid control arm (ie, specific treatment group or placebo) and conduct a randomized, controlled study.

As described in Section 2.2, based on the AGAVE-201 study results, axatilimab 0.3 mg/kg Q2W IV showed the most favorable benefit:risk profile among 3 dose groups in participants with cGVHD who had received 2 or more lines of prior therapy. The pivotal study did not include any Japanese participants; therefore, this study is intended to confirm the safety and efficacy of axatilimab 0.3 mg/kg Q2W IV in the Japanese cGVHD population.

The primary objective of this study is to evaluate ORR during the first 6 cycles of treatment as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD. The criteria are widely used for evaluating efficacy of treatment of cGVHD. The primary endpoint, ORR by Day 169 or Cycle 7 Day 1 (whichever is later), has been selected to allow for robust evaluation of efficacy and consistency with AGAVE-201.

2.2.2. Justification for Dose

All participants will receive axatilimab 0.3 mg/kg Q2W administered as a 30-minute (−5 to +10 minutes) IV infusion via an infusion pump. This is the same dose and administration method as in the AGAVE-201 study.

Based on Study INCA 34176-101, which evaluated the safety, tolerability, and PK of a single dose of axatilimab in healthy Japanese participants, axatilimab 0.3 mg/kg and 1.0 mg/kg were well tolerated, and no specific safety concerns were identified. When Study INCA 34176-101

was compared with Study SNDX-6352-0001 in non-Japanese participants, no differences were observed in PK or ADA profiles between races.

For pediatric participants, body weight–adjusted doses (mg/kg), similar to the general clinical pediatric dose calculation (Temrikar et al 2020), will be administered. The potential of antibody products to predict PK in pediatric participants at least 6 years of age is based on adult data, and how to define pediatric volume with body weight–adjusted doses has been discussed in published literature (Xu et al 2020).

Based on the above, axatilimab 0.3 mg/kg Q2W IV, the recommended dose that demonstrated favorable safety and efficacy in AGAVE-201, can be safely administered to Japanese participants with cGVHD as long as they are carefully monitored according to the Protocol-specified tests and observation schedule.

2.2.3. Brief Epidemiology of Disease Studied and Minority Populations

Chronic GVHD is a rare disease in Japan. Approximately 37% of patients develop cGVHD within 2 years after allo-HSCT (JSTCT 2022). Approximately 3900 allo-HSCT cases were reported in Japanese patients in 2020 (JDCHCT 2023). It is therefore estimated that approximately 1440 patients develop cGVHD per year.

The number of pediatric patients with cGVHD in Japan is very low. The incidence of cGVHD in pediatric patients is reported to be lower than that in adults (Baird et al 2010). The number of Japanese pediatric patients with cGVHD is unknown, but the number of allo-HSCTs performed in pediatric patients (aged 14 years or younger) in 2020 was approximately 270, which is less than 10% of all allo-HSCTs in Japan (JDCHCT 2023).

2.3. Benefit/Risk Assessment

To date, available axatilimab nonclinical and clinical data support clinical investigation in Japanese participants with cGVHD. Based on the pharmacologic and toxicologic properties of axatilimab, predicted AEs include periorbital edema, facial swelling, infusion reactions, and pruritus.

Due to its mechanism of action (pharmacological inhibition of CSF-1R), axatilimab may induce dose-dependent and reversible increases in circulating levels of CPK, AST, ALT, glutamate dehydrogenase, amylase, and lipase (refer to the IB for details). Kupffer cells in the liver (which are involved in the clearance of these enzymes) are in the macrophage lineage and are susceptible to axatilimab inhibition of CSF-1R. Observed transient elevations of serum enzymes were consistent with the described effect of CSF-1R inhibition of Kupffer cell–mediated enzymatic clearance. The expected increases in these enzyme levels are related to decreased clearance from the blood rather than from DILI and are not associated with any histopathological change. Laboratory assessments (ie, serum chemistry, including tests for liver function) will be performed to monitor participant safety. To minimize exposure to ionizing radiation in pediatric and adolescent participants, bone density assessments will be performed only at screening, on Day 1 of every sixth cycle, and at EOT.

Thus far, data have shown clinical responses across all axatilimab dose levels evaluated in a pretreated cGVHD population in both a Phase 1/2 study (SNDX-6352-0503) and the AGAVE-201 study. The pivotal study identified 0.3 mg/kg Q2W IV as the most favorable risk:benefit treatment among 3 dose cohorts. This study design aims to confirm benefit from axatilimab in Japanese participants with cGVHD and reduce unnecessary risk while closely monitoring participant safety.

Given the scientific basis for testing CSF-1R–targeted therapy in cGVHD, the proportion of patients with cGVHD who do not respond to available front-line treatments or cannot fully benefit from them due to toxicities, the lack of treatment options for patients with relapsed cGVHD, and a study design intended to confirm the clinical benefit and tolerability of axatilimab seen in the AGAVE-201 study, the risk of axatilimab 0.3 mg/kg Q2W IV in the proposed population is justified.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of axatilimab may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: 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 ADAs

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall 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 and discontinued due to progression of disease, intolerability, or toxicity. Disease progression is defined 1) by the NIH 2014 consensus criteria, either in terms of an organ-specific algorithm or a global assessment or 2) as active, symptomatic cGVHD for which the physician believes a new line of systemic therapy is required.

The study will consist of the following 3 periods: screening, treatment, and follow-up. Throughout the study, participants will be evaluated as specified in the SoA (see Table 3).

After signing the ICF, potential candidates will undergo screening procedures to determine eligibility.

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. On-treatment responses will be assessed using the NIH 2014 consensus criteria (CR, PR, or lack of response [unchanged, mixed, or progression]) Q4W and at the EOT visit. When the decision is made to discontinue study treatment, participants will have an EOT visit then a safety follow-up visit 30 days after the EOT visit.

For participants who continue to derive clinical benefit, study drug administration may be continued until axatilimab receives marketing authorization in Japan.

Participants who achieve CR or PR and subsequently discontinue study treatment due to a reason other than disease progression will have recurring disease follow-up visits for a maximum of 24 months from Cycle 1 Day 1. A primary efficacy analysis will be performed when all participants have had the opportunity to complete 6 cycles of treatment of axatilimab.

All participants who are receiving study drug at the time of marketing authorization in Japan will then discontinue study treatment and complete the EOT and safety-follow up visits.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the study.

The study will include up to 28 days for screening, continuous treatment in consecutive 28-day cycles as long as participants are receiving benefit and have not met any criteria for discontinuation of study drug, and 30 days (+ 7 days) for safety follow-up after the EOT visit. It is estimated that an individual will participate for approximately 8 to 10 months.

Once the study drug has received marketing authorization, study treatment will be discontinued for all participants who are receiving axatilimab at that time and the EOT and safety follow-up visits will be conducted. The sponsor will inform each principal investigator in advance of the timing of treatment discontinuation.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study site contract. The investigator/head of the study site is to notify the IRB/IEC in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, if, for example, required by regulatory decision or for sponsor decision to not further develop the compound. If the study is terminated, the sponsor will notify the investigators/head of the study site, IRBs, IECs, and regulatory bodies of the decision and reason for termination. The decision from the sponsor will be via the head of the study site(s), who will notify the investigators and the IRBs of the decision and reason for termination of the study.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in this Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. At least 6 years of age at the time of signing the ICF.
2. Ability to comprehend and willingness to sign a written ICF for the study.
    - For participants 6 to 17 years old, a parent/guardian must provide consent for pediatric participants; when applicable, pediatric participants should also sign an assent form.
3. Japanese participants who are allo-HSCT recipients with active, refractory, or recurrent cGVHD requiring systemic immune suppression despite at least 2 lines of prior systemic therapy.
    - Active cGVHD is defined as the presence of signs and symptoms of cGVHD per the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD (Jagasia et al 2015).
    - Refractory disease is defined as meeting any of the following criteria:
        – The development of 1 or more new sites of disease while being treated for cGVHD.
        – Progression of existing sites of disease despite at least 1 month of standard or investigational therapy for cGVHD.
        – Participants who did not achieve a response within 3 months on prior therapy for cGVHD and for whom the treating physician believes a new systemic therapy is required.
    - Recurrent cGVHD is defined as active, symptomatic disease (after an initial response to prior therapy) based on the NIH 2014 consensus criteria (Lee et al 2015) by organ-specific or global assessment or for which the physician believes a new line of systemic therapy is required.
4. Participants may have persistent, active aGVHD and cGVHD manifestations (overlap syndrome), as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD.
5. Karnofsky performance score of ≥ 60 (if aged 16 years or older); Lansky performance score of ≥ 60 (if aged younger than 16 years).

6. Adequate organ and bone marrow functions evaluated during the 14 days prior to the start of study treatment as follows:
    a. Absolute neutrophil count ≥ 1.0×10^9/L (without growth factors within 1 week of Cycle 1 Day 1).
    b. Platelet count ≥ 50×10^9/L (without growth factor or transfusion within 2 weeks of Cycle 1 Day1).
    c. ALT and AST ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN.
    Note: For participants with suspected or documented liver cGVHD: ALT and AST ≤ 5 × ULN and total bilirubin ≤ 1.5 × ULN.
7. Creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault formula in adult participants and Schwartz formula in pediatric participants.
8. Concomitant use of a systemic corticosteroid is allowed but not required. Topical and inhaled corticosteroid agents are allowed. If a participant is taking a corticosteroid, it must be a stable dose for at least 2 weeks prior to the start of study treatment.
9. Concomitant use of CNIs or MMF is allowed but not required (the CNI or MMF may have been started either for prophylaxis or for treatment of cGVHD the reason for initiating treatment must be recorded in the database). If a participant is taking a CNI or MMF, the following criteria must be met:
    a. Must be a stable dose for at least 2 weeks prior to the start of study treatment.
    b. The dose must be within the therapeutic range.
10. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last dose of study treatment and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative pregnancy test before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last dose of study treatment and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. Female participants not considered to be of childbearing potential as defined in Appendix A are eligible.

5.2. Exclusion Criteria

Participants will be excluded from the study if any of the following criteria apply:

1. Has aGVHD without manifestations of cGVHD.
2. Any evidence (histologic, cytogenetic, molecular, hematologic, or mixed) of relapse of the underlying cancer or post-transplant lymphoproliferative disease at the time of screening.
3. History of acute or chronic pancreatitis.
4. History of myositis.
5. History or other evidence of severe illness, uncontrolled infection, allergy to excipients (see formulation details in the IB), or any other conditions that would make the participant, in the opinion of the investigator, unsuitable for the study.
6. Has acquired immunodeficiency syndrome.
7. History of latent or active TB, including either one of following:
   a. Signs or symptoms suggestive of active TB upon medical history and/or physical examination.
   b. Recent close contact with a person with active TB.
8. Positive QuantiFERON® and/or T-spot TB test at screening.
9. Active HBV or HCV infection that requires treatment, or at risk for HBV reactivation (ie, positive HBsAg). Participants with negative HBsAg and positive total HBcAb and/or HBsAb should be excluded if quantitative HBV DNA test result is ≥ 20 IU/mL (1.3 logIU/mL) at the time of screening. Participants who are positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
10. Diagnosed with another malignancy (other than malignancy for which transplant was performed) within 3 years before Cycle 1 Day 1 unless previously treated with curative intent (eg, completely resected basal cell or squamous cell carcinoma of the skin, resected in situ cervical malignancy, resected breast ductal carcinoma in situ, or low-risk prostate cancer after curative resection) and approved by the sponsor's medical monitor.
11. Pregnant or breastfeeding.
12. Previous exposure to CSF-1R targeted therapies.
13. Use of any agent other than corticosteroids, CNIs, or MMF for the treatment of cGVHD within 2 weeks or 5 half-lives, whichever is shorter, prior to the start of study treatment.
14. Has received an investigational treatment within 28 days prior to the start of study treatment.
15. Currently participating in any other interventional study.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Recruitment Strategy and Retention of Participants

This study is designed to evaluate the efficacy and safety of axatilimab in the Japanese population, and there is no specific recruitment plan for racial or ethnic diversity.

This study will be conducted at Japanese medical institutions that specialize in the treatment of hematologic malignancies as well as HSCT. As described in Section 2.2.3, a limited number of pediatric participants is expected; therefore, this study may also include hospitals that specialize in pediatric treatment.

5.6. Replacement of Participants

The sponsor and investigator may decide to replace participants who do not meet the eligibility requirements or who have significant Protocol deviations.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Table 6 presents the study treatment information.

Table 6: Study Treatment Information

Study treatment name	Axatilimab (INCA034176)
Mechanism of action	CSF-1R mAb
Dose formulation	Solution for infusion
Unit dose strength(s)/ dose level(s)	50 mg/mL per vial/0.3 mg/kg
Administration instructions	IV infusion via an infusion pump over 30 minutes upon dilution in 0.9% normal saline solution; time windows of – 5 minutes to + 30 minutes are permitted (ie, infusion time may be 25-60 minutes). The exact duration of infusion should be recorded in both source documents and eCRFs.
Packaging and labeling	Axatilimab is supplied as a 1.3-mL (1-mL extractable volume) sterile, preservative-free solution in 2R, colorless, Type I, glass vials closed with a rubber stopper and sealed with an aluminum overseal and flip-off cap. The vials are single-use only. Each vial will be labeled as required per country requirement.
Storage	Axatilimab should be stored at 5°C ± 3°C. Do not freeze. Protect from light.
Status of treatment in participating countries	Investigational

Axatilimab will be provided to the site centrally by the sponsor or designated representative.

6.2. Preparation, Handling, and Accountability

The investigator, investigational drug storage manager, or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator, investigational drug storage manager, and authorized site staff.

The investigator, investigational drug storage manager, or designee is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any

applicable regulatory authorities. The investigator, investigational drug storage manager, or designee must maintain records that document the following:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug, including vial counts and lot numbers and/or vial numbers (as applicable) of study drug used to prepare the infusion solution from each supply dispensed.

The investigational product must be used only in accordance with the Protocol. The investigator, investigational drug storage manager, or designee will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator, investigational drug storage manager, or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator, investigational drug storage manager, or designee will oversee the destruction of any remaining study drug according to institutional SOPs. If, however, local procedures do not allow on-site destruction, shipment of the study drug back to the sponsor is allowed. In this case, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for preparation and final disposition of unused study treatments are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using IRT. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. Full details will be provided in the IRT Study Reference Manual.

This is an open-label study; no comparisons will be made between participants or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study.

Compliance with study drug administration will be calculated by the sponsor based on study drug accountability and infusion records documented by the site staff and monitored by the sponsor/designee.

For the first 2 axatilimab infusions, a mandatory 2-hour observation period for potential IRRs is required. For subsequent infusions and per the discretion of the investigator, participants who have had no IRRs may be observed for a shorter period of at least 30 minutes. Participants who have an IRR at any time must continue to undergo the mandatory 2-hour observation period after each infusion.

The dose should be recalculated if the participant's body weight increases or decreases by > 10% from baseline. Otherwise, the dose should remain unchanged.

6.5. Stopping Rules and Dose Modifications

Instructions for dose modifications for axatilimab are outlined in Table 7. Individual decisions regarding dose modifications of axatilimab should be made using clinical judgment in consultation with the sponsor's medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

Table 7: Dose-Reduction Levels for Axatilimab

Starting dose	0.3 mg/kg Q2W IV
Reduction of 1 dose level	0.2 mg/kg Q2W IV
Reduction of 2 dose levels	0.15 mg/kg Q2W IV

Participants who do not tolerate therapy after 2 dose-level reductions from the starting dose must be withdrawn from the study. Once the axatilimab dose has been reduced for reasons of toxicity, it cannot be re-escalated. Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed with sponsor approval. The acceptable length of interruption will depend on agreement between the investigator and the sponsor's medical monitor.

All dose modifications should be documented appropriately. Investigators may take a more conservative approach than the guidelines outlined in the Protocol if, based on their clinical judgment, it is in the best interest of the participant. Such instances should be reported to the sponsor's medical monitor.

6.5.1. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Treatment with axatilimab may be delayed up to 4 weeks (28 days) to allow for resolution of toxicity. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any participant whose treatment has been delayed for more than 28 days before restarting treatment with axatilimab.

Individual decisions regarding dose reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the

study drug and the participant's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

Each toxicity is graded by the investigator according to NCI CTCAE v5.0.

6.5.1.1. Elevation of AST, ALT, Bilirubin, CPK, Amylase, or Lipase

Dose modification guidelines for axatilimab due to AST, ALT, bilirubin, CPK, amylase, or lipase elevation are specified in Table 8.

Table 8: Dose Modification Guidelines for Axatilimab Based on Laboratory Results

Toxicity	Action
On the day of dose administration	
Asymptomatic Grade 2 AST or ALT (3.0-5.0 × ULN if baseline was normal; 3.0-5.0 × baseline if baseline was abnormal), with ≤ Grade 1 total bilirubin	Continue axatilimab without dose delay or reduction with agreement from both the investigator and sponsor's medical monitor.
Grade 3 AST or ALT (5.0-20.0 × ULN if baseline was normal; 5.0-20.0 × baseline if baseline was abnormal) with total bilirubin ≤ Grade 1	Hold axatilimab dose until recovery to Grade 2, then resume axatilimab at the next lower dose (see Table 7).
Regardless of the time of the event	
Concurrent ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN in the absence of cholestasis (elevation of ALP and GGT > 2.5 × ULN)	Permanently discontinue axatilimab.
Grade 4 AST or ALT (> 20 × ULN)	Permanently discontinue axatilimab.
Grade 2 total bilirubin	Hold axatilimab dose until recovery to Grade 1, then resume axatilimab at the same dose level.
Grade 3 total bilirubin	• Hold axatilimab dose until recovery to Grade 1 or baseline, then resume axatilimab at the next lower dose (see Table 7). • If recovery cannot be achieved within 4 weeks of last dose, axatilimab should be permanently discontinued. • If Grade 3 occurs again, despite a dose reduction, axatilimab should be permanently discontinued.
≥ Grade 3 CPK, amylase, or lipase in the absence of any clinical symptoms	• Before administering axatilimab, conduct diagnostic evaluation (eg, serum and urine myoglobin or CPK-MB, BUN, creatinine, ECG, and troponin [I or T]). • If results show no evidence of end-organ damage, continue axatilimab without dose reduction with agreement from both investigator and sponsor's medical monitor. • If the results show evidence of end-organ damage, axatilimab should be permanently discontinued.
Symptomatic Grade 3 CPK, amylase, or lipase	Permanently discontinue axatilimab with agreement from both investigator and sponsor's medical monitor.
Axatilimab can cause modulation of Kupffer cells in the liver, which may lead to elevation of liver enzymes (ALT and AST). Serum bilirubin, ALP, and GGT will need to be monitored along with ALT and AST for assessment of liver toxicity.	

Note: Grade is per NCI CTCAE v5.0.

6.5.1.2. Other Nonhematologic Toxicities

The rules for the management of other nonhematologic toxicities are outlined in Table 9 with toxicities graded by the investigator according to NCI CTCAE v5.0.

Table 9: Other Nonhematologic Toxicities: Dose Modification Guidelines for Axatilimab

Toxicity	Action
Grade 4	• Administer symptomatic remedies/start prophylaxis. • Permanently discontinue axatilimab.
Grade 3	• Administer symptomatic remedies/start prophylaxis. • Hold axatilimab dose until recovery to Grade 2 under the following directions: – If axatilimab is held for ≤ 4 weeks, resume axatilimab at the next lower dose (see Table 7). – If axatilimab is held for > 4 weeks, permanently discontinue axatilimab.
Grade 2	• Administer symptomatic remedies/start prophylaxis. • Do not hold axatilimab dose.

Note: Grade is per NCI CTCAE v5.0.

6.5.1.3. Hematologic Toxicities: Dose Modification Guidelines for Axatilimab

The guidelines in Table 10 will be followed for determining dose modifications based on hematologic status at the time of planned dose administration.

Table 10: Hematologic Toxicities: Dose Modification Guidelines for Axatilimab

Toxicity	Action
• Grade 3 to 4 neutropenia, febrile neutropenia, neutropenic infection, or uncomplicated thrombocytopenia • Grade 2 complicated thrombocytopenia	Hold axatilimab dose until recovery to Grade 1 or study baseline under the following directions: • If axatilimab is held for ≤ 4 weeks, resume axatilimab at the next lower dose (see Table 7). • If axatilimab is held for > 4 weeks, permanently discontinue axatilimab.
Recurrence of the same hematologic toxicity	If the **same** hematologic toxicity **recurs**: • Administer symptomatic remedies/start prophylaxis. Hold axatilimab dose until recovery to Grade 1 or baseline. • If recovered within 14 days, resume axatilimab at next lower dose (see Table 7). • If not recovered within 14 days despite axatilimab dose reduction to next lower dose, as described above, permanently discontinue axatilimab. • If the third episode, permanently discontinue axatilimab.

Note: Grade is per NCI CTCAE v5.0.

6.5.1.4. Infusion-Related Reaction

Participants receiving study drug should be monitored for signs and symptoms of IRRs (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate or blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).

Participants who have an IRR should be managed per institutional standard of care. Treatment recommendations for axatilimab IRRs are outlined in Table 11.

Participants who have an axatilimab IRR may continue on axatilimab treatment per guidance presented in Table 11. Participants who previously had an IRR will receive a premedication regimen of diphenhydramine and acetaminophen 25 to 50 mg IV (or oral equivalent; per institutional guidelines) approximately 30 to 60 minutes prior to each subsequent dose of axatilimab.

If a Grade 2 IRR does not improve or worsens after implementation of the modifications indicated in Table 11 (including reducing the infusion rate by 50%), the investigator may consider treatment with corticosteroids, and the infusion should be stopped for that day. At the next cycle, administration of oral premedication with an antihistamine and antipyretic is required. Prophylactic corticosteroids are not permitted. When corticosteroids are used for the treatment of severe reactions, the corticosteroid dose should be tapered to baseline within 14 days.

Premedication for IRR prophylaxis may be substituted for the site-standard regimen only if the sponsor's medical monitor agrees.

If the participant has a second IRR of Grade 2 or higher on the slower 50% infusion rate, with or without the addition of further medication to the mandatory premedication, the infusion should be stopped, and the participant should be discontinued from study treatment.

Table 11: Guidance for Treatment of Infusion-Related Reactions

Grade	Dose Modification	Toxicity Management
Grade 1 or 2	**For Grade 1:** The infusion rate of axatilimab should be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of axatilimab should be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions should be given at 50% of the initial infusion rate.	• Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. • Consider premedication per institutional standard prior to subsequent doses. • Corticosteroids should not be used for routine premedication of IRRs ≤ Grade 2.
Grade 3 or 4	Permanently discontinue axatilimab	Manage severe IRRs per institutional standards (eg, epinephrine intramuscular followed by diphenhydramine and ranitidine IV and glucocorticoid IV).

Note: Grade is per NCI CTCAE v5.0.

6.5.1.5. Change to Dose Schedule for Axatilimab

Participants who have had their Cycle 7 Day 1 assessment and have achieved a PR or CR that has been sustained for at least 20 weeks and have not progressed may change their dose schedule from Q2W to Q4W. Their new dose regimen will be 0.6 mg/kg Q4W IV. Changes to the dose schedule are not considered dose escalations as the dose intensity remains unchanged.

Treatment assessment visits for participants with the Q4W dose schedule are not required for the Cycle 7+ Day 15 visits (see Table 3).

6.5.2. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying disease will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- The occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- An AE requiring more than 2 dose reductions (0.15 mg/kg of axatilimab).
- A persistent AE requiring a delay of therapy for more than 4 weeks (28 days) unless a greater delay has been approved by the sponsor.

See Section 7 for discontinuation procedures.

6.5.3. Discontinuation of Study Drug for Lack of Efficacy

Study drug should be discontinued if a participant does not achieve a PR or CR within 9 months of Cycle 1 Day 1. However, a participant may continue on study treatment if the investigator/treating physician believes that the participant is deriving clinical benefit and if the participant reports clinically meaningful symptomatic improvement (that may not be captured by the NIH criteria).

Any participant who has an unequivocal progression of cGVHD (eg, initiation of new systemic therapy for cGVHD or increase in corticosteroid, CNI, or MMF dose beyond those allowed by Protocol) at any time should have their treatment discontinued.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any medication received up to 28 days before the first dose of study drug and 30 days after the EOT visit, or until the participant begins a new cGVHD therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered for treatment of SAEs (as defined in Section 9.2) should be recorded even if the SAE is reported beyond 30 days after the EOT visit. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

Topical therapies (including topical corticosteroids) that the investigator considers necessary for a participant's plan of care may be administered concomitantly with axatilimab at the investigator's discretion per standard of care. Other supportive medications in accordance with standard clinical practice (such as for prophylaxis for encapsulated bacteria, viral, or fungal infections) are permitted per institutional policy.

Premedication with 25 to 50 mg IV or oral equivalent diphenhydramine and acetaminophen approximately 30 to 60 minutes prior to each dose of axatilimab may be administered in accordance with standard site practice in the absence of prior infusion related reactions.

6.6.1.1. Corticosteroids

Participants may be taking a corticosteroid upon study entry. At the discretion of the investigator, the corticosteroid dose may be tapered after the first 4 weeks of study drug administration for participants who achieve either a PR or CR. It is strongly recommended that corticosteroids are tapered at a rate of no more than 25% of the daily dose Q4W and that they are tapered prior to discontinuation of any concomitant CNI or MMF.

If corticosteroids have been tapered, 1 re-escalation is allowed at the discretion of investigator. The re-escalation of corticosteroids during the first 6 cycles from the start of axatilimab should follow the below guidelines:

- Re-escalation of corticosteroids can be performed up to the baseline dose if the baseline dose was a total daily dose of < 0.9 mg/kg prednisone or equivalent.
- The re-escalation dose should be a maximum total daily dose of 0.9 mg/kg if the baseline dose was ≥ 0.9 mg/kg.

For Cycle 7 onwards, in the case of exacerbation of cGVHD, participants may have an increased corticosteroid dose of up to a maximum total daily dose of 0.9 mg/kg prednisone or equivalent for a period of no longer than 8 weeks.

Concomitant corticosteroid details during the study treatment period (eg, dose and regimen) must be reported in the specific eCRF page.

6.6.1.2. Calcineurin Inhibitors and Mycophenolate Mofetil

Participants may be taking a CNI or MMF upon study entry. The dose on Cycle 1 Day 1 must have been stable for at least 2 weeks (Inclusion Criterion 9). After the first postbaseline assessment, a participant's CNI or MMF dose may be modified. Reasons for modification are as follows:

- To maintain a therapeutic dose. In this case, the CNI or MMF may be increased above the dose at Cycle 1 Day 1.
- For a cGVHD flare. In this case, the dose of CNI or MMF may be increased once above the dose at Cycle 1 Day 1.
- If participant is receiving a fixed dose of a CNI or MMF, and a new medication is started that significantly changes their metabolism. In this case, dose modification may be pursued following established evidence (eg, decrease in tacrolimus dose by one-third upon initiation of voriconazole). Reasons for this change must be documented in the eCRF.

A substitute CNI or MMF cannot be started unless a change is indicated by toxicity or intolerance attributable to the prior CNI or MMF. Such substitutions may include a change from one CNI to another CNI, one MMF to another MMF, a CNI to an MMF, or an MMF to a CNI, at the discretion of the investigator. The reasons for this change must be documented in the eCRF.

If after 4 weeks of study treatment the participant achieves a PR or CR, the dose of CNI or MMF may be reduced or discontinued; for such cases, doses may be subsequently re-escalated for flare of cGVHD to no more than the dose at Cycle 1 Day 1. At the discretion of the treating physician and aligned with institutional policy, it is recommended that the concomitant CNI or MMF be tapered after the tapering of any concurrent corticosteroid.

Concomitant CNI and MMF details during study treatment must be reported in the specific eCRF page. Information reported on CNI should include drug name, target trough level, measured trough level, and actual dose.

6.6.2. Restricted Medications and Procedures

Vaccines, other than live vaccines, which are prohibited (see Section 6.6.3), should be administered on a week that does not coincide with axatilimab infusion.

Biologic therapies (eg, IV immunoglobulins, mAbs) used for non-antineoplastic and non-cGVHD causes are permitted. However, they should be administered on a week that does not coincide with axatilimab infusion.

Use of systemic corticosteroids to treat acute non-cGVHD conditions (eg, anaphylaxis, adrenal crisis) is allowed as clinically indicated, provided that the steroid dose can be tapered to baseline within 14 days.

6.6.3. Prohibited Medications and Procedures

The following are prohibited:

- Immune-suppressive agents for the treatment of cGVHD.
  - Exceptions: Systemic corticosteroids, CNIs, and MMF.
  - Note: This does not include agents for the treatment of aGVHD or the acute manifestations of overlap syndrome.
- Live-virus vaccines.
- Antineoplastic systemic chemotherapy or biological therapy.
  - Note: Concomitant use of medications indicated for maintenance therapy targeting the participant's previously treated underlying malignancy is allowed. This includes but is not limited to the use of proteasome inhibitors (eg, ixazomib), endocrine therapies (eg, tamoxifen, exemestane), and tyrosine kinase inhibitors (eg, sorafenib, imatinib).
- Investigational agents other than axatilimab.
- Corticosteroids for infusion reaction prophylaxis.
- Radiation therapy.
- Traditional herbal medicines. These therapies are not fully studied, and it is unknown whether their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity.

6.7. Continued Access to Study Drug After the End of the Study

Upon completion of the study, participants may be prescribed the best standard of care available.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

It may be necessary for a participant to permanently discontinue study treatment prior to the planned completion of the treatment regimen (see Sections 6.5.2 and 6.5.3). If study treatment is permanently discontinued, the participant will remain in the study to be evaluated for safety (up to 30 days from EOT) and cGVHD (until unequivocal progression) follow-up. See Table 3 for data to be collected at EOT.

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons:

- The participant becomes pregnant.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in the public domain, may be solicited from or collected on the participant. Consent may also be partial. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Progressive disease or exacerbation of any of the signs or symptoms of the disease as assessed by the investigator.
- Unacceptable toxicity as noted in Section 6.5.2.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A participant **may** be discontinued from study treatment as follows:

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be discontinued from study treatment.
- If a participant is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3 and Table 4. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The EOT visit should be performed and date recorded.
- The status of the participant should be updated to EOT in the IRT
- Participants must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

See Table 3 and Table 4 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally designated representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted.
  - Informed consent must be obtained using the most current IRB/IEC-approved version in a language that is native and understandable to the participant. An ICF template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template, and all site-specific changes must be approved by the IRB/IEC and the sponsor or its designee. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements including optional samples/procedures (eg, optional biopsy) and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the country in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that their personal data collected for the study will be used in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- A copy of the ICF(s) must be provided to the participant's legally designated representative.
- The participant's legally designated representative must be informed that participation in the study is voluntary. The participants' legally designated representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the country in which the study is being conducted as well as the IRB/IEC or study center.
- The authorized person (the legally designated representative) obtaining the informed consent must sign the ICF.

Participants who are rescreened are required to sign a new ICF and will be assigned a new participant number.

8.1.2. Legal Guardian Consent and Pediatric Participant Assent Processes

- The investigator, or a person designated by the investigator, will provide the legal guardian with the written ICF and the participant with the assent, if applicable. They must be informed that participation is voluntary. The legal guardian will be required to sign written consent, and the participant, if applicable, will be required to sign written assent that meets the requirements of local regulations and ICH guidelines where applicable, and the IRB/IEC or study center after the nature of the study has been fully explained and before performance of any study-related activity.
- Assent requirements for pediatric participants may vary across regions and countries; local regulations should be followed as appropriate.
- The medical record must include a statement that written informed consent from the legal guardian and assent from the pediatric participant (if deemed appropriate by local ethics review or local regulations) were obtained before the participant was enrolled in the study and the date the written consent and assent were obtained. The medical record should describe how the clinical investigator determined that the person signing the ICF was the participant's legal guardian. The authorized person obtaining the informed consent must also sign the ICF and assent form attesting that the pediatric participant did not show signs of dissent; it should be written in language appropriate to the child's developmental and functional status.
- Participants and their legal guardian must be reconsented and reassented to the most current version of the ICF(s) during their participation in the study.

8.1.3. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (Cycle 1 Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 28 days of Cycle 1 Day 1). For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine eligibility. Treatment should start as soon as possible but within 3 days after the date of IRT enrollment.

See Sections 5.4 and 5.6 for information regarding screen failures and replacement of participants, respectively.

8.1.4. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the country's abbreviation, the site ID, and the participant number. Site staff should contact the IRT to obtain the participant ID number during screening.

Upon determining that the participant is eligible for study entry, the IRT will be contacted to obtain the study drug number. Additionally, the IRT will be contacted at the study visits indicated in Table 3 to update the study drug supply. Additional details will be provided in the IRT manual.

8.1.5. Distribution of Study Participation Card

Participants will be provided with a study participation card at enrollment. The study participation card will indicate but not be limited to the expected study period, emergency contact information, prohibited and restricted medications, and precautions to take during the study. The card is to be presented to medical institutions other than the study site to inform other institutions of study participation, prevent Protocol deviations (eg, prescription of prohibited concomitant drugs), and ensure the safety of participants.

The card must be reviewed and approved by the IRB as per the study site's SOP.

8.1.6. Demography and Medical History

8.1.6.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical

history, and current illnesses. Medical history will include relevant medical and surgical treatments within the last 10 years that are considered to be clinically significant by the investigator.

8.1.6.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's primary hematologic disease, including date of diagnosis, prior therapy, disease stage at the time of transplantation, disease risk index (Armand et al 2014; see Appendix G), characteristics of allo-HSCT, and history of GVHD, will be recorded.

8.1.7. Chronic GVHD Diagnosis and Staging at Screening

Diagnosis of cGVHD will be established using NIH diagnostic criteria outlined in Appendix C. The global severity of cGVHD will be assessed as mild, moderate, or severe according to established NIH consensus criteria based on the number and severity of each organ involvement (mouth, GI, lungs, eyes, joints and fascia, liver, skin, genital tract; Jagasia et al 2015; see Appendix D). All organs must be assessed and scored using NIH scoring criteria (see Appendix D).

8.2. Efficacy Assessments

It is preferred that all cGVHD assessments be performed by the same person who completed the Cycle 1 Day 1 assessments. At a minimum, the Cycle 7 Day 1 assessments should be performed by the same person who performed the Cycle 1 Day 1 assessment. In addition, any assessments leading to changes in cGVHD therapy must be confirmed by the investigator or treating physician.

8.2.1. Response Determination According to 2014 NIH Consensus Definitions

Physician-assessed responses will be evaluated as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD (Lee et al 2015). Complete response is defined as resolution of all manifestations in each organ or site, and PR is defined as improvement in at least 1 organ or site without progression in any other organ or site. Table 12 contains the consensus definitions of CR, PR, and progression for assessment of organ-specific responses as well as a global response determination.

Table 12: Response Determination for Chronic GVHD Based on Clinical Assessment

Organ	Complete Response	Partial Response	Progression
Skin	NIH skin score of 0 after previous involvement	Decrease in NIH skin score by 1 or more points	Increase in NIH skin score by 1 or more points, except from 0 to 1
Eyes	NIH eye score of 0 after previous involvement	Decrease in NIH eye score by 1 or more points	Increase in NIH eye score by 1 or more points, except from 0 to 1
Mouth	NIH modified OMRS of 0 after previous involvement	Decrease in NIH modified OMRS by 2 or more points	Increase in NIH modified OMRS by 2 or more points
Esophagus	NIH esophagus score of 0 after previous involvement	Decrease in NIH esophagus score by 1 or more points	Increase in NIH esophagus score by 1 or more points, except from 0 to 1
Upper GI	NIH upper GI score of 0 after previous involvement	Decrease in NIH upper GI score by 1 or more points	Increase in NIH upper GI score by 1 or more points, except from 0 to 1
Lower GI	NIH lower GI score of 0 after previous involvement	Decrease in NIH lower GI score by 1 or more points	Increase in NIH lower GI score by 1 or more points, except from 0 to 1
Liver	Normal ALT, ALP, and total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	Normal $\%FEV_1$ after previous involvement If PFT unavailable, NIH lung symptom score of 0 after previous involvement	Increase by 10% predicted absolute value of $\%FEV_1$ If PFT unavailable, decrease in NIH lung symptom score by 1 or more points	Decrease by 10% predicted absolute value of $\%FEV_1$ If PFT unavailable, increase in NIH lung symptom score by 1 or more points, except from 0 to 1
Joints and fascia	NIH joint and fascia score of 0 and P-ROM score of 25 after previous involvement by at least 1 measure	Decrease in NIH joint and fascia score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH joint and fascia score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score of 0	Decrease in clinician overall severity score by 2 or more points on a 0-10 scale	Increase in clinician overall severity score by 2 or more points on a 0-10 scale

Source: Lee et al 2015.

8.2.2. Response Determination for Pediatric Participants

No special assessments will be performed for pediatric patients. However, for pediatric participants who are unable to comply, PFT assessments will include pulse oximetry and as clinically indicated, and include a computed tomography scan with inspiratory and expiratory phases to assess air trapping, which will be included in the response evaluation.

8.2.3. Physician-Reported Global and Organ-Specific cGVHD Activity Assessments

Changes in cGVHD severity as defined by the 2014 NIH consensus criteria will be evaluated using the physician-reported global and organ-specific cGVHD activity assessment forms (see Appendix D and Appendix E). The clinicians will provide a subjective assessment of current overall cGVHD severity on a 10-point categorical scale (eg, none, mild, moderate, severe) independent of the recorded NIH global severity score (see Table 12), and their evaluations of

cGVHD changes since the last assessment. Key organ assessments include skin, mouth, liver, upper and lower GI, esophagus, lung, eye, and joint/fascia (Jagasia et al 2015, Lee et al 2015).

8.2.4. Participant-Reported cGVHD Activity Assessment (mLSS)

Changes in participant-reported symptom activity will be evaluated using the cGVHD mLSS (Lee et al 2002, Teh et al 2020), which has been recommended for use by the 2005 and 2014 NIH consensus conferences to capture cGVHD symptoms.

The cGVHD mLSS questionnaire (see Appendix F) asks participants to indicate the degree of "bother" during the past 7 days due to symptoms in 7 domains (skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, emotional distress) potentially affected by cGVHD (Lee et al 2002). Published evidence supports its validity, reliability, and sensitivity to cGVHD severity (Lee et al 2015, Merkel et al 2016, Teh et al 2020).

8.2.5. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

8.3. Safety Assessments

See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study drug or until the start of new cGVHD therapy. Adverse events for enrolled participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or surrogate). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, that are considered related to the study drug/procedures, or that caused the participant to discontinue the study drug. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?", is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be reported to the sponsor or designee by the investigator immediately without undue delay and not later than 24 hours of obtaining knowledge of the events. The investigator

will also submit any updated SAE data to the sponsor immediately without undue delay and not later than 24 hours of obtaining knowledge of the update.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, a physician assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the visits indicated in Table 3, a comprehensive physical examination should be conducted. The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

During the treatment and disease follow-up periods, participants will have targeted physical examinations. Participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the Adverse Events Form in the eCRF.

For participants who are at least 18 years of age, height will be measured at screening only. For participants younger than 18 years of age, height will be measured at screening, Cycle 3 Day 1, and then every third cycle.

Weight will be measured at screening, Day 1 of every cycle, EOT, and safety follow-up.

8.3.3. Vital Signs

Vital sign measurements (to be taken before infusion of study drug and blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, and body temperature. For the first 2 infusions, vital sign measurements should also be performed during and after infusion. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in a recumbent, semirecumbent, or sitting position after 5 minutes of rest.

Abnormal vital sign results identified after the first dose of study drug constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug.

8.3.4. Neurological Examination

A neurological examination will include general appearance, posture and gate, motor activity, assessment of mental status, cranial nerves, sensory and neuromuscular function, and reflexes.

8.3.5. Karnofsky/Lansky Performance Status

The Karnofsky/Lansky performance status allows participants to be classified as to their functional impairment on a scale from 0 to 100 (see Table 13). The lower the score, the worse the survival for most serious illnesses. The score can be used to compare effectiveness of different therapies and to assess the prognosis in individual participants. The Karnofsky scale is designed for participants aged 16 years and older, and the Lansky scale is designed for participants younger than 16 years (Lansky et al 1987). The Karnofsky scale is a widely used, validated tool in oncology settings, especially HSCT (Crooks et al 1991, O'Toole and Golden 1991, Schag et al 1984).

Table 13: Karnofsky/Lansky Performance Status Scale

Score	Karnofsky[a]	Lansky[b]
	Able to carry on normal activity; no special care is needed	**Able to carry on normal activity; no special care is needed**
100	Normal, no complaints, no evidence of disease	Fully active
90	Able to carry on normal activity, minor signs or symptoms of disease	Minor restriction in physically strenuous play
80	Normal activity with effort, some signs or symptoms of disease	Restricted in strenuous play, tires more easily, otherwise active
	Unable to work, able to live at home, cares for most personal needs, a varying amount of assistance is needed	**Mild to moderate restriction**
70	Cares for self, unable to carry on normal activity or do active work	Both greater restrictions of and less time spent in active play
60	Requires occasional assistance, but is able to care for most of his/her needs	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	Considerable assistance required for any active play, fully able to engage in quiet play
	Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly	**Moderate to severe restriction**
40	Disabled, requires special care and assistance	Able to initiate quite activities
30	Severely disabled, hospitalization indicated; Death not imminent	Needs considerable assistance for quiet activity
20	Very sick, hospital indicated, death not imminent	Limited to very passive activity initiated by others (eg, watching television)
10	Moribund, fatal processes progressing rapidly	Completely disabled, not even passive play
0	Death	Death

[a] For participants aged 16 years and older.
[b] For participants younger than 16 years.

8.3.6. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the SoA (see Table 3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or discontinue study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.7. Laboratory Assessments

See Appendix B for the list of clinical laboratory tests to be performed and Table 4 for the timing and frequency. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, lipid panel, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 28 days before Cycle 1 Day 1. If performed more than 7 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1.

Laboratory sample collection on Cycle 1 Day 1 must be performed before study treatment administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration (within the 3-day window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

8.3.8. Bone Turnover Markers

Soluble bone markers, including BAP and CTX, will be measured as indicated in Table 4. A central laboratory will perform the BAP and CTX assessments and report the results to the study site.

During the treatment period, samples will be collected on Day 1 of each cycle for up to a maximum of 2 years. For participants who continue treatment for more than 2 years, sample collection at the EOT visit is not applicable.

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

8.3.9. Bone Density DEXA Scan

Monitoring of bone density will be performed using a DEXA scan. Any DEXA scans collected within 6 months prior to the participant's enrollment in the study can be considered as the screening assessment. During the treatment period, DEXA scans will be performed on Cycle 7 Day 1, on Day 1 of every sixth cycle (± 7 days) thereafter, and at the EOT visit (if not performed in the preceding 6 months; see Table 3).

8.3.10. Pulmonary Function Tests

Age-appropriate PFTs will be performed to determine the $\%FEV_1$ during the screening period as the lung baseline status. If a PFT is performed within 7 days before Day 1, the results can be used as baseline for cGVHD response assessments (ie, the test is not required to be repeated at Cycle 1 Day 1). For participants with documented lung involvement, from Cycle 7 onward, PFTs should be performed at the same visit as cGVHD response determination (Day 1 of Cycles 7-12 and Q8W [± 7 days] thereafter) and at the EOT visit. In addition, clinical symptoms will be assessed for lung score, which is used for response assessment.

8.3.11. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening, on Day 1 (before the first dose of study drug), and at the EOT visit, and at the safety follow-up visit. Urine pregnancy tests will be performed locally as outlined in Table 4, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement. If a urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.

For WOCBP, monthly telephone visits should take place to check pregnancy status (via testing, including home pregnancy tests) during the period when contraception is mandatory (ie, from screening through 30 days after the EOT).

If the serum pregnancy test result is negative after a urine test result was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study drug and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test result, see Section 9.8 for reporting requirements.

8.3.12. Serology

8.3.12.1. Hepatitis Screening

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Appendix B. Generally, hepatitis tests should be

performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

For participants with positive HBcAb and/or HBsAb but with negative HBV DNA (< 20 IU/mL [1.3 logIU/mL]), an HBV DNA quantitative test should be performed at least once every 3 months according to the Hepatitis B Treatment Guidelines (JSH 2023).

8.3.12.2. HIV Screening

For participants with unknown HIV status, an HIV-1/2 antibody test will be performed at the screening visit.

8.3.12.3. Tuberculosis Screening

A TB screening test will be performed at the screening visit. Negative QuantiFERON and/or T-spot should be confirmed to rule out TB infection.

8.3.13. Chimerism and Graft Failure

Donor chimerism after an allo-HSCT identifies the genetic profiles of the recipient and the donor pretransplant and then evaluates the ratio of donor-to-recipient cells in the recipient's blood or bone marrow. Chimerism testing using peripheral blood or bone marrow will be performed at the treating investigator's discretion according to local institutional practice.

Participants will be monitored for evidence of graft failure during study treatment and posttreatment follow-up according to local institutional practices. Graft failure will be defined as> 95% recipient cells with no signs of relapse.

If a participant experiences graft failure, any action taken to manage the graft, including rapid taper of immunosuppression, administration of nonscheduled donor lymphocyte infusion, stem cell boost, or other intervention(s), should be recorded in the appropriate eCRF.

8.4. Pharmacokinetic Assessments

Axatilimab levels in plasma samples will be determined using a validated enzyme-linked immunosorbent assay.

A maximum of 4 samples including those for immunogenicity assessments (ADA) may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. Samples collected for analyses of axatilimab plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. The actual date and time (24-hour clock time) of each sample will be recorded. Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual.

8.4.1. Blood Sample Collection

Timing of blood PK and immunogenicity assessments is outlined in Table 4 and Table 14. After the predose PK sample is drawn, participants will begin the study treatment. Adjustments to the timing of blood sampling may be made based on emerging PK data.

Table 14: Pharmacokinetic and Antidrug Antibody Blood Sample Timing

Study Visit	Assessment	Timing of Sample
Cycle 1 Day 1	PK and ADA	Preinfusion
	PK	• 30 minutes (end of infusion, + 10 minutes) • 2 hours (± 15 minutes) after the start of infusion • 6-8 hours after the start of infusion
Cycle 1 Day 8	PK	Any time
Cycle 2 Day 1	PK and ADA	Preinfusion
	PK	• 30 minutes (end of infusion, + 10 minutes) • 2 hours (± 15 minutes) after the start of infusion • 6-8 hours after the start of infusion
Day 1 of every other cycle, from Cycle 4 up to Cycle 12	PK and ADA	Preinfusion
Day 1 of every 4 cycles, for Cycles ≥ 12 (up to 2 years from Cycle 1 Day 1)	PK and ADA	Preinfusion
Follow-up (EOT + 30 days) (not applicable after 2 years)	PK and ADA	Any time

Note: Preinfusion is within 24 hours before the start of infusion (within 2 hours before the start of infusion at Cycle 1 Day 1).

8.4.2. Immunogenicity Assessments

Antibodies to axatilimab will be evaluated in plasma samples collected from all participants according to Table 4 and Table 14. Additionally, plasma samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Plasma samples will be screened for antibodies binding to axatilimab, and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to axatilimab and/or further characterize the immunogenicity of axatilimab.

The detection and characterization of antibodies to axatilimab will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to study drug will also be evaluated for axatilimab plasma concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug. Samples may be stored for a maximum of 10 years from the first CSR for study-related research (or according to local regulations) at a facility selected by the sponsor to enable further analysis of immune responses to study treatment.

8.5. Pharmacodynamic and Translational Assessments

Pharmacodynamic and translational assessments will be performed according to Table 4 and Table 15. 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.

Table 15: Biomarker/Translational Sample Timing

Study Visit	Assessment	Timing of Sample
Cycle 1 Day 1 Cycle 1 Day 8 Cycle 2 Day 1 Cycle 4 Day 1	Serum biomarker Whole blood PBMC	Preinfusion on Day1 and then any time on Cycle 1 Day 8
EOT (not applicable after 2 years)	Serum biomarker Whole blood PBMC	Any time

Note: Preinfusion is within 24 hours before the start of infusion (within 2 hours before the start of infusion at Cycle 1 Day 1).

8.5.1. Whole Blood PBMC for Pharmacodynamic Assessments

Whole blood will be analyzed for levels of circulating monocyte subsets at baseline and longitudinally. The activity observed will be compared with the exposure of the compound and safety endpoints. Other methods to confirm this analysis may be performed based on emerging data.

[redacted]

8.5.2. Serum for Biomarker Assessments

Serum will be collected to analyze IL-34 and CSF-1 as well as other [redacted] biomarkers and change from baseline compared with PK and safety endpoints.

8.6. Storage and Future Use of Biological Samples

Biological samples (eg, biomarkers, pharmacodynamics, PK) may be stored from the date of the last participant's last visit to perform study-related research. Additional research outside of study-related research will not be performed. Pseudonymized participant samples will be transported to the sponsor or designated vendor for analysis as detailed in the laboratory-specific study manual(s). All samples for BAP and CTX will be destroyed immediately following analysis. Pharmacokinetic, biomarker, and pharmacodynamic samples may be stored for up to 10 years from the first CSR for study-related research unless otherwise agreed with national regulatory requirements in participating countries and/or local health authorities in separate site and/or participant documents.

8.7. Unscheduled Visits

Unscheduled study visits may occur at any time during the study if medically warranted. Data from all assessments performed at unscheduled visits must be recorded in the eCRF.

8.8. End of Treatment

When the participant permanently discontinues study drug, whether the participant is withdrawing from the study early or the participant has completed the study, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visit.

8.9. Follow-Up

8.9.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 37 days after the EOT visit (of after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug. Ongoing AEs/SAEs must be followed up until toxicities resolve, return to baseline, or are deemed irreversible. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period.

If a participant is scheduled to begin a new cGVHD therapy before the end of the safety follow-up period, the safety follow-up visit should be performed before a new cGVHD therapy is started.

If any AEs considered study drug–related are unresolved at the time of the safety follow-up visit, reasonable efforts should be made to follow the AEs until toxicities resolve, return to baseline, or are deemed irreversible.

8.9.2. Post-Treatment Disease Follow-Up

Participants will continue to be followed for cGVHD response after the EOT visit if all the following conditions are met:

- Participant is in CR or PR at EOT.
- Participant completed study treatment taper or discontinued study treatment for reasons other than cGVHD progression and with no requirement for new cGVHD therapy.

Participants will be monitored for cGVHD response until cGVHD progression, initiation of a new cGVHD therapy, death, or the end of the study and for a maximum of 24 months from Cycle 1 Day 1.

See Table 3 for additional details with regard to timepoints and assessments.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related. • An AE can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to disease progression) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, decreased platelet count). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition that develops after the start of study drug is to be reported as an AE. • New conditions detected or diagnosed after the start of study drug administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Overdose (accidental or intentional) is to be reported as an AE. Additionally, signs and/or symptoms resulting from overdose and signs and/or symptoms resulting from a medication error are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will **not** be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • Signs and/or symptoms resulting from clinically significant abnormal laboratory findings associated with the underlying disease, or signs and/or symptoms resulting from consequences of expected disease progression, can be reported as an AE if judged by the investigator to be more severe than expected (eg, not compared with baseline) for the participant's condition or participant's disease progression. – If a participant has an ongoing condition from their medical history that worsens during the study but due to progressive disease, it will not be considered an AE. For example, if a participant has congestive heart failure as part of their medical history and it **worsens** during the study due to progressive disease, it (ie, worsening of congestive heart failure) is not an AE if the severity is not worse than expected for disease progression in the medical and scientific judgment of the investigator.

- A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history.
- Pre-existing diseases, pre-existing conditions, or new conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization or death due to disease progression).

If an overdose meets serious criteria, the overdose term should be reported as an SAE. Additionally, signs and/or symptoms resulting from an overdose are to be reported as an SAE if serious criteria are met.

If a medication error event meets serious criteria, the medication error term should be reported as an SAE. Additionally, signs and/or symptoms resulting from a medication error are to be reported as an SAE if serious criteria are met.

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been **admitted** as an inpatient at the hospital or emergency department for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Emergency department visits that do not result in admission to the hospital should be evaluated for one of the other serious criteria (eg, life-threatening, required intervention to prevent permanent impairment or damage, other medically important event). Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE.

Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) is not considered an SAE.

d. Results in persistent or significant disability/incapacity

The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers; intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered SAEs.

An event that may lead to disability is also considered an important medical event. It includes a case that is exposed to a risk of dysfunction to an extent that interferes with daily life when the adverse drug reaction occurs. It does not include an adverse drug reaction that, had the reaction been more severe, may have caused disability.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Events Form in the eCRF. All AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF. For detailed information, refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or designee) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Events Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Incyte Reference Guide for Completing the SAE Report Form.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine the following:

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug as a result of the AE/SAE(s).

- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Events Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age-appropriate activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB for the study drug in making their assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change their opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- Once an AE is detected, it should be followed in the Adverse Events Form in the eCRF until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology.
- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (SAE eCRF via the EDC system [primary method], or by completing the SAE form and sending via email/fax [only if the EDC system is unavailable]) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) immediately without undue delay but not later than 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedure), all SAEs occurring after the participant has signed the ICF through the safety visit or at least 30 days after the last dose of study drug must be reported to the sponsor (or designee) immediately without undue delay but not later than **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately without undue delay but not later than 24 hours of obtaining knowledge of the update.

This information must also be reported immediately to the head of the study site.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or more than 30 days after the last dose of study drug. If the investigator learns of any SAE, including death, at any time during this period, and they consider the event to be reasonably related to the study drug or study participation, then the investigator must notify the sponsor (or designee) immediately but no later than 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor regarding an SAE is essential so that legal obligations and ethical responsibilities for the safety of participants and the safety of a study drug under clinical investigation are met.

If the SAE is not documented in the RSI of the IB for the study drug (new occurrence) and is thought to be related to the study drug, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees as applicable following the sponsor's (or approved designee) SOPs in accordance with national regulatory requirements in participating countries.

The sponsor will report suspected expected deaths and life-threatening events to the PMDA as per local regulatory requirements.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety report notifications must be prepared by the sponsor for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Events Form in the eCRF.
- The investigator must report immediately but no later than 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for notifying Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor without undue delay but not later than 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. Once the EDC system is functional, the SAE report should be retroactively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form for details and for the email address or fax number).
- Incyte Pharmacovigilance will issue queries for missing or discrepant information directly into the applicable EDC system (primary method) or via the Data Clarification Form (only if the EDC system is not available).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Potential Drug-Induced Liver Injury

In the event a participant has 1) an increase in ALT or AST elevation ≥ 3 × ULN, 2) a total bilirubin > 2 × ULN, and 3) an ALP < 2 × ULN, clinical tests (eg, blood and imaging tests) must be performed frequently as per standard of care until resolution and/or stabilization (see Appendix H). In addition, a diagnostic workup must be performed to exclude alternative causes such as viral hepatitis, pre-existing chronic or acute liver disease or abnormalities, liver location of chronic graft-versus-host disease, the administration of other drug(s) known to be hepatotoxic or confirmed Hy's law.

Follow the SAE and follow-up reporting requirements per Section 9.2 as potential DILI AEs may be potential SAEs classified in the category of important medical event.

9.6. Events of Clinical Interest

An ECI is an AE (serious or nonserious) that Incyte wishes to document in an organized manner for monitoring or understanding. An ECI does not require rapid communication by an investigator to Incyte unless it meets criteria for rapid communication as an SAE (see Section 9.2). An ECI may be captured in a special way (eg, tick box) in the eCRF.

Infusion-related reactions (including hypersensitivity reactions), pneumonitis, serum enzyme elevations, periorbital edema, anemia, thrombocytopenia, infections, and viral infections will be considered ECIs for this study.

9.6.1. Adverse Events of Special Interest

Not applicable.

9.7. Emergency Unblinding of Treatment Assignment

Not applicable.

9.8. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure safety:

- The study drug must be discontinued immediately (female participants only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee immediately but no later than **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluations. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be

recorded on the same form. This form should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form or Study Reference Manual for further details.

Any SAE occurring during the pregnancy of a study participant must be recorded and reported as described in Section 9.4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.9. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study as necessary. If new significant risks are identified, they will be added to the ICF.

9.10. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or their designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

If the investigator is asked to return the product for investigation, they will return a copy of the product complaint communication with the product.

Complaints associated with unapproved medical devices will be reported to the sponsor with a Medical Device Defect Report Form, and the sponsor will report medical device defects to the PMDA as per local regulatory requirements.

9.11. Treatment of Overdose

Overdose (accidental or intentional) is to be reported as an AE (see Section 9.1). Medication errors are to be reported as an AE. If the overdose meets serious criteria, the overdose term should be reported as an SAE (see Section 9.2). Additionally, signs and/or symptoms resulting from overdose are to be reported as an AE/SAE.

For this study, any dose of study drug greater than 3.6 mg/kg within a 24-hour time period will be considered an overdose and recorded in the eCRFs.

Incyte does not recommend specific treatment for an overdose. Overdose with concomitant medication treatment will not be recorded in the eCRFs unless it resulted in an AE.

In the event of an overdose, the investigator should do the following:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study drug can no longer be detected systemically (at least 45 days).
- Obtain a plasma sample for PK analysis within 14 days from the date of the last dose of study drug, if requested by the medical monitor or if possible (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

There has been no clinical experience with overdose of axatilimab (study drug). Treatment of overdose should consist of general supportive measures.

10. STATISTICS

10.1. Sample Size Determination

Approximately 20 participants will be enrolled and will receive axatilimab 0.3 mg/kg Q2W IV.

[redacted]

10.2. Populations for Analysis

The populations for analysis are provided in Table 16.

Table 16: Populations for Analysis

Population	Description
FAS	The FAS will include all participants who received at least 1 dose of study drug. The FAS will be used for both efficacy and safety analyses in this study.
PK/pharmacodynamic evaluable	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).

10.3. Level of Significance

This is an exploratory study, and no formal statistical tests will be performed. All CIs will be 95%.

10.4. Statistical Analyses

10.4.1. Primary Analysis

The primary efficacy endpoint is the ORR in the first 6 cycles, calculated based on objective response, defined as having CR or PR at any timepoint up to Cycle 7 Day 1 and before the start of additional systemic therapy for cGVHD. Response will be assessed according to the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD (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 discontinued the study. Participants without postbaseline response assessments will be considered as nonresponders. All cGVHD assessments will be censored at the start of additional systemic therapy for cGVHD.

10.4.2. Secondary Analysis

The proportion of participants with a ≥ 7-point reduction in mLSS score will be provided together with 95% CIs.

The ORR, together with 95% exact binomial CIs, will be provided for the duration of the study.

Duration of response will be assessed for responders only and is defined as the time from the first response of PR or CR until cGVHD progression, death, or the date of additional systemic therapy for cGVHD. Participants without an event will be censored at the last valid response assessment before the data cutoff or additional systemic therapy for cGVHD. 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.

The organ-specific response rate, together with 95% CIs, will be provided for each individual organ per 2014 NIH criteria.

Participants who discontinue corticosteroids as well as participants with a percentage reduction of corticosteroid dose will be summarized by visit.

10.4.2.1. Pharmacokinetics

Pharmacokinetic analyses will be performed for the PK-evaluable population. Axatilimab concentration data will be summarized by visit and time.

If there is a sufficient amount of concentration data from this study, it will be analyzed by standard population PK methods using appropriate software (eg, Monolix). Otherwise, the data will be pooled with data from other studies for a population PK analysis.

10.4.2.2. Antidrug Antibody Immunogenicity

Samples for ADA analysis classified as negative, positive, or missing and the proportion of participants classified as negative, treatment-emergent positive, or persistent treatment-emergent positive will be summarized. The proportion of participants who are neutralizing antibody–positive and have treatment-emergent positive ADA status will also be summarized.

10.4.3. Safety Analyses

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

10.4.3.1. Adverse Events

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. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration.

Adverse events will be tabulated by MedDRA system organ class and preferred term. Severity of AEs will be based on NCI CTCAE v5 using Grades 1 through 5. 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.

An overall summary of AEs will include the number (%) of participants reporting any TEAEs, any SAEs, any Grade 3 or higher TEAEs, any treatment-related TEAEs, any fatal TEAEs, and any TEAEs leading to interruption, reduction, or discontinuation of study drug.

10.4.3.2. Clinical Laboratory Tests

The clinical laboratory data will be analyzed using summary statistics. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated. Potential DILIs will be listed. The criteria for determining potential DILIs will be provided in the Statistical Analysis Plan.

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated. The following summaries will be produced for the laboratory data:

- Number and percentage of participants with worst postbaseline CTCAE grade (regardless of baseline value). Each participant will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.
- For laboratory parameters in which CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classification based on laboratory reference ranges.
- Change in bone turnover markers (ie, BAP and CTX) as well as T-scores and Z-scores from bone density scans.

10.4.3.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (ie, blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities, and participants exhibiting clinically notable vital sign abnormalities will be listed.

10.4.3.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria. Participants exhibiting clinically notable ECG abnormalities will be listed.

[redacted]

10.5. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator. All documents must be reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from the IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Recording and documenting AEs or laboratory abnormalities identified in the Protocol as critical to the safety evaluation and reporting them to the sponsor according to the reporting requirements specified in the Protocol.
  - Recording and documenting all AEs, unless the Protocol provides different guidance in Section 9.
  - Reporting to the sponsor all SAEs occurring in participants treated by them in the clinical study unless the Protocol provides different guidance in Section 9.
  - Reporting an SAE to the sponsor per Section 9 procedures and timelines if they become aware of an SAE with a suspected causal relationship to the study drug that occurs after the end of the study.
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Ensuring (along with the sponsor) that the clinical study is conducted in accordance with the Protocol and with the principles of GCP.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
  - Assigning tasks among the members of the team of investigators in a way that does not compromise the safety of participants or the reliability and robustness of the data generated at the clinical study site.

- The investigator will adhere to the Protocol as described in this document and agree that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
  - The investigator will retain the content of the clinical trial master file, essential documents, AE documentation, and medical and other study records in accordance with all local, national, and regulatory laws but for a minimum period of at least 30 years after completion or discontinuation of the study or as described in the final executed copy of the individual site agreement, or at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after formal discontinuation of clinical development of the test article and the regulatory authority is notified, whichever is longer, to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.
- The record retainer (delegated by the head of the study site) will retain the J-GCP–defined essential documentation at this site until the regulatory approval of the study drug or at least 3 years after the discontinuation or completion of the study conduct, whichever is longer. If the sponsor requires retention of these documents for a longer period of time, the duration and method of retention will be decided upon through discussion between the sponsor and the study site. It is the responsibility of the sponsor to inform the head of the study site as to when the documents no longer need to be retained.

11.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any country or region, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, the sponsor must be informed immediately.

In addition, the investigator will inform the sponsor immediately of any urgent safety measures taken to protect study participants against immediate hazard and of any serious breaches of this Protocol or of ICH GCP.

While "immediately" cannot be defined by the clinical trial regulations with hours and a fixed number of days for every situation, it does imply prompt action. The urgency and nature of the situation should determine the appropriate timeframe for action (eg, 1 business day vs 2 business days).

11.1.2. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of their responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, study charters, or biomarker plans, as applicable.

The sponsor (or designee) will be responsible for the following:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated and/or collected, including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for the following:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, biomarker data, photographs, diary data) or as otherwise specified in the Protocol.

- Maintaining adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.

- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.

- Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
- Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Quality tolerance limits will be predefined in the Operational Manual to identify systematic issues that can impact participants' safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

11.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, disclosure, and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws including additional local regulations will be included in relevant study agreements. Description of measures that will be implemented in case of a data security breach will be reported to the competent authorities, ethics committees, and data participants within the time specified and in accordance with applicable GDPR, local laws, and regulations to prevent further damage/spread.

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. There may be certain duly authorized and contracted

vendors managing participants' services such as for travel and meal reimbursement, home delivery services, and/or parking, in which case those vendors will have the participant's directly identifiable personal information but in no circumstances will that directly identifiable information be transferred or sent to the sponsor. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law, relevant study agreements, and current local regulations.

11.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research participants, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.6. Publication Policy





11.7. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time at the sole discretion of the sponsor or the IRB/IEC. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

When the study is completed, the investigator should inform the head of the study site of the completion in writing and submit a written summary of the study's outcome, and then the head of the study site should promptly inform the IRB and sponsor or designee of the completion in writing.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Further, reasons for the early closure of a study site (eg, premature termination) by the sponsor, investigator, or IRB/IEC may include but are not limited to the following:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures or site agreement, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.
- Circumstances beyond the control of the sponsor or investigator that make it unreasonable to require the continuation of the study or site.
- Failure to carry out the study in the interest of the health of the participants.
- Failure to demonstrate that the continuation of an IRB-/IEC-approved study (ie, the IRB/IEC had previously issued a positive decision on the study) has scientific merit.
- Financial reasons (eg, the sponsor is declared insolvent or a bankruptcy petition has been filed).

12. REFERENCES

Alexander KA, Flynn R, Lineburg KE, et al. CSF-1-dependant donor-derived macrophages mediate chronic graft-versus-host disease. J Clin Invest 2014;124:4266-4280.

Armand P, Gibson CJ, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood 2012;120:905-913.

Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood 2014;123:3664-3671.

Axatilimab Investigator's Brochure. Wilmington, DE: Incyte Corporation.

Baird K, Cooke K, Schultz KR. Chronic graft-versus-host disease (GVHD) in children. Pediatr Clin North Am 2010;57:297-322.

Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. 2020.

Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354:1813-1826.

Crooks V, Waller S, Smith T, Hahn TJ. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol 1991;46:M139-M144.

Cutler CS, Koreth J, Ritz J. Mechanistic approaches for the prevention and treatment of chronic GVHD. Blood 2017;129:22-29.

Flowers ME, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. Blood 2011;117:3214-3219.

Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. Blood 2015;125:606-615.

Imbruvica (ibrutinib) [prescribing information]. Pharmacyclics LLC; May 2023.

Inamoto Y, White J, Ito R, et al. Comparison of characteristics and outcomes of late acute and NIH chronic GVHD between Japanese and white patients. Blood Adv 2019;3:2764-2777.

Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015;21:389-401.

Japan Society of Hepatology. Hepatitis B Treatment Guidelines (4th edition). Accessed December 15, 2023. https://www.jsh.or.jp/medical/guidelines/jsh_guidlines/hepatitis_b.html

Japanese Data Center for Hematopoietic Cell Transplantation. Hematopoietic cell transplantation in Japan. 2021 National Survey Report. Accessed December 15, 2023. https://www.jdchct.or.jp/data/report/2021

Japanese Society for Transplantation and Cellular Therapy. GVHD Guidelines. 5th ed. Japan; 2022.

Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. Cancer 1987;60:1651-1656.

Lee JH, Lee JH, Choi SJ, et al. Graft-versus-host disease (GVHD)-specific survival and duration of systemic immunosuppressive treatment in patients who develop chronic GVHD following allogeneic hematopoietic cell transplantation. Br J Haematol 2003;122:637-644.

Lee SJ, Flowers ME. Recognizing and managing chronic graft-versus-host disease. Hematology Am Soc Hematol Educ Program 2008:134-141.

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.

Lee SJ, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2002;8:444-452.

MacDonald KP, Hill GR, Blazar BR. Chronic graft-versus-host disease: biological insights from preclinical and clinical studies. Blood 2017;129:13-21.

Merkel EC, Mitchell SA, Lee SJ. Content validity of the Lee Chronic Graft-versus-Host Disease Symptom Scale as assessed by cognitive interviews. Biol Blood Marrow Transplant 2016;22:752-758.

Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood 2017;130:2243-2250.

Niederwieser D, Baldomero H, Szer, J, et al. Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the Worldwide Network for Blood and Marrow Transplantation Group including the global survey. Bone Marrow Transplant 2016;51:778-785.

O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. West J Med 1991;155:384-387.

Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2:187-193.

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.

Temrikar ZH, Suryawanshi S, Meibohm B. Pharmacokinetics and clinical pharmacology of monoclonal antibodies in pediatric patients. Paediatr Drugs 2020;22:199-216.

Xu Y, Langevin BA, Zhou H, Xu Z. Model-aided adults-to-children pharmacokinetic extrapolation and empirical body size-based dosing exploration for therapeutic monoclonal antibodies-is allometry a reasonable choice? J Clin Pharmacol 2020;60:1573-1584.

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

WOCBP: A woman who is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Female participants on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)

The following are **not** acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method
- Male condom with cap, diaphragm, or sponge with spermicide
- Male and female condom used together

Note: Men with a pregnant or breastfeeding partner must agree to use a male condom during each episode of penile penetration.

For female participants who are WOCBP

The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
- Intrauterine device[d]
- Intrauterine hormone-releasing system[d]
- Bilateral tubal occlusion[d]
- Vasectomized partner[d,e]

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

[b] If the male participant has a partner of childbearing potential, the partner should also use contraceptives.

[c] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method. In this case, 2 methods of contraception should be used.

[d] Contraception methods that in the context of this guidance are considered to have low user dependency.

[e] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.

Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. REQUIRED LABORATORY ANALYTES

<table>
<tr><th>Blood Chemistries</th><th>Hematology</th><th>Urinalysis With Microscopic Examination[a]</th><th>Serology</th><th>Coagulation</th></tr>
<tr><td rowspan="4">Albumin
ALP
ALT
AST
Amylase
BUN
Calcium
Chloride
CPK
Creatinine
Glucose
GGT
Lactate dehydrogenase
Lipase
Magnesium[b]
Phosphate
Potassium
Sodium
Total bilirubin
Direct and indirect bilirubin[c]
Total protein</td><td rowspan="4">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• WBC count

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils

Absolute and/or percent values must be provided for:
• WBC differential (including with any abnormal cell types)</td><td>Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein
Urobilinogen</td><td>HBsAg
HBsAb
HBcAb
HBV DNA[d]
HCVAb
HCV RNA[e]
HIV[f]
TB[g]</td><td>PT
aPTT[h]
INR</td></tr>
<tr><th></th><th>Lipid Panel</th><th>Bone Turnover Markers[i]</th><th>Pregnancy Testing</th></tr>
<tr><td>Total cholesterol
Triglycerides
LDL
HDL</td><td>BAP
CTX</td><td>FSH[j]
hCG[k]</td></tr>
</table>

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.

[a] Full analysis should be performed at screening and EOT. During the treatment period, microscopic examination is to occur if blood is suspected in urine.
[b] At screening only unless clinically indicated.
[c] Direct and indirect bilirubin required for participants with elevated total bilirubin.
[d] If applicable.
[e] Polymerase chain reaction is required and must be negative for HCV RNA in participants who are positive for HCV antibody.
[f] If HIV status is unknown.
[g] At screening only.
[h] QuantiFERON or T-spot test.
[i] Centrally measured.
[j] Serum; for female participants only to confirm nonchildbearing potential.
[k] Serum and urine; WOCBP only.

APPENDIX C. STAGING OF CHRONIC GVHD (NIH CRITERIA)

The definitions of for mild, moderate, and severe cGVHD are as follows:

Mild cGVHD

- 1 or 2 organs involved with no more than score of 1

  plus

- Lung score of 0

Moderate cGVHD

- 3 or more organs involved with no more than score of 1

  or

- At least 1 organ or site with a maximum score of 2

  or

- Lung score of 1

Severe cGVHD

- At least 1 organ with a score of 3

  or

- Lung score of 2 or 3

Key points:

- In skin: higher of the 2 scores to be used for calculating global severity.
- In lung: FEV_1 is used instead of clinical score for calculating global severity.
- If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
- If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes), the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Staging of cGVHD as described by Jagasia et al (2015) should be performed using scoring criteria as described in Appendix D. Only organs with active cGVHD signs and symptoms at baseline can be considered as affected by cGVHD and reported as such at study entry.

APPENDIX D. ORGAN-SPECIFIC SEVERITY SCORING

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS**				
Symptom score:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: % FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*†) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)



ADL = activities of daily living; ALT = alanine aminotransferase; AP = alkaline phosphatase; BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky performance status; LFTs = liver function tests; LPS = Lansky performance status; ULN = upper limit of normal.

* Weight loss within 3 months.

† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total BSA score and the skin feature score, or if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

‡ To be completed by specialist or trained medical providers.

** Lung scoring should be performed using both the symptoms and FEV_1 scores whenever possible. FEV_1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV_1 scores.

APPENDIX E. GLOBAL CHRONIC GVHD ACTIVITY ASSESSMENT (CLINICIAN REPORT)

The response assessment is based on the NIH guideline to measure therapeutic response in cGVHD (Lee et al 2015). For an overall response assessment, it is required to assess the status of all organs at each timepoint, including those organs that are not involved at baseline.

Given that cGVHD symptoms recorded during disease response assessment can frequently be impacted by a variety of clinical conditions common in the cGVHD patient population (eg, worsened shortness of breath could be related to an acute infection; liver chemistry abnormalities to recent initiation of a new drug, such an azole), careful evaluation and scrutiny of the etiology is necessary at every response. As specified by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD (Lee et al 2015), if it is felt that a change in findings is entirely related to the non-cGVHD etiology, the affected organ is to be considered nonevaluable at the particular timepoint.

The following assessments shown in the form below are to be performed when clinically relevant:

- Bronchiolitis obliterans
  - Force vital capacity (FVC)
  - DLCO (adjusted for hemoglobin)
  - Total lung capacity (TLC)
  - Residual volume (RV)
- Baseline values
  - Total distance walked in 2 or 6 minutes

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** — **Most severe cGvHD symptoms possible**	**Over the <<time>> would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Mouth	**Erythema**	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
								Total score for all mucosal changes	

Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)	TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 min		Karnofsky or Lansky	Platelet Count K/uL	Total WBC K/uL	Eosinophils %

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe … Most severe symptoms possible				
EYES	☐ No symptoms symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
LUNGS	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

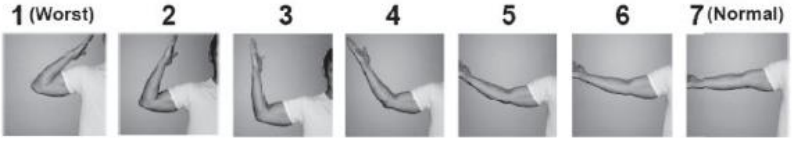
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	☐ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	☐ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

Shoulder



❑ Not done

Elbow



❑ Not done

Wrist/finger



❑ Not done

Ankle



❑ Not done

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

APPENDIX F. CHRONIC GVHD MODIFIED LEE SYMPTOM SCALE

Please let us know if you have been bothered by any of the following problems in the last 7 days.

Subscale	Item	Not at all	Slightly	Moderately	Quite a bit	Extremely
Skin	a. Abnormal skin color	0	1	2	3	4
	b. Rashes	0	1	2	3	4
	c. Thickened skin	0	1	2	3	4
	d. Sores on skin	0	1	2	3	4
	e. Itchy skin	0	1	2	3	4
Eye	f. Dry eyes	0	1	2	3	4
	g. Need to use eye drops frequently	0	1	2	3	4
	h. Difficulty seeing clearly	0	1	2	3	4
Mouth	i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
	j. Ulcers in mouth	0	1	2	3	4
Lung	k. Frequent cough	0	1	2	3	4
	l. Colored sputum	0	1	2	3	4
	m. Shortness of breath at rest	0	1	2	3	4
	n. Fevers	0	1	2	3	4
Nutrition	o. Difficulty swallowing solid foods	0	1	2	3	4
	p. Difficulty swallowing liquids	0	1	2	3	4
	q. Vomiting	0	1	2	3	4
	r. Weight loss	0	1	2	3	4
Energy	s. Shortness of breath with exercise	0	1	2	3	4
	t. Joint and muscle aches	0	1	2	3	4
	u. Limited joint movement	0	1	2	3	4
	v. Muscle cramps	0	1	2	3	4
	w. Weak muscles	0	1	2	3	4
	x. Loss of energy	0	1	2	3	4
	y. Need to sleep more/take naps	0	1	2	3	4
Psych	z. Depression	0	1	2	3	4
	aa. Anxiety	0	1	2	3	4
	bb. Difficulty sleeping	0	1	2	3	4

Source: Lee et al 2002, Teh et al 2020.

APPENDIX G. DISEASE RISK INDEX

Disease at Diagnosis	Stage at the Time of Transplant	Disease Risk Index Group
Hodgkin lymphoma CR	—	Low
Hodgkin lymphoma PR	—	Intermediate
Hodgkin lymphoma	Advanced[a]	High
CLL CR	—	Low
CLL PR	—	Low
CLL	Advanced[a]	Intermediate
Mantle cell lymphoma CR	—	Low
Mantle cell lymphoma PR	—	Intermediate
Mantle cell lymphoma	Advanced[a]	High
Indolent B-cell NHL[b] CR	—	Low
Indolent B-cell NHL[b] PR	—	Low
Indolent B-cell NHL[b]	Advanced[a]	Intermediate
T-cell NHL CR	—	Intermediate
T-cell NHL PR	—	Intermediate
T-cell NHL	Advanced[a]	High
Aggressive B-cell NHL[c] CR	—	Intermediate
Aggressive B-cell NHL[c] PR	—	Intermediate
Aggressive B-cell NHL[c]	Advanced[a]	Very high
AML favorable cytogenetics CR	—	Low
AML favorable cytogenetics	Advanced[a]	High
AML intermediate cytogenetics CR	—	Intermediate
AML intermediate cytogenetics	Advanced[a]	High
AML adverse cytogenetics CR	—	High
AML adverse cytogenetics	Advanced[a]	Very high
CML chronic phase 1/2	—	Low
CML advanced phase	—	Intermediate
CML blast phase	—	Very high
Myeloproliferative neoplasm or CMML	Any	Intermediate
ALL CR1	—	Intermediate
ALL CR2	—	High
ALL CR3	—	High
ALL	Advanced[a]	Very high
High-risk MDS[d] adverse cytogenetics	Early[e]	High
High-risk MDS[d] intermediate cytogenetics	Early[e]	Intermediate
High-risk MDS[d] intermediate cytogenetics	Advanced[a]	High
High-risk MDS[d] adverse cytogenetics	Advanced[a]	High

Disease at Diagnosis	Stage at the Time of Transplant	Disease Risk Index Group
Low-risk MDS[f] adverse cytogenetics	Early[e]	Intermediate
Low-risk MDS[f] adverse cytogenetics	Advanced[a]	High
Low-risk MDS[f] intermediate cytogenetics	Early[e]	Intermediate
Low-risk MDS[f] intermediate cytogenetics	Advanced[a]	Intermediate
Burkitt lymphoma CR		High
Burkitt lymphoma PR	Advanced[a]	Very high
Multiple myeloma CR/VGPR/PR	—	Intermediate
Multiple myeloma	Advanced[a]	High

ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; CMML = chronic myelomonocytic leukemia; NHL = non-Hodgkin lymphoma; VGPR = very good partial response.

[a] Advanced stage refers to induction failure or active relapse, including stable or progressive disease for NHL, Hodgkin lymphoma, and CLL.

[b] Indolent B-cell NHL includes follicular lymphoma, marginal zone lymphoma, and lymphoplasmacytic lymphoma. Small lymphocytic lymphoma is included in the CLL group.

[c] Aggressive B-cell NHL includes diffuse large B-cell lymphoma and transformed indolent B-cell lymphoma.

[d] High-risk MDS refers to MDS with > 5% blasts (RAEB-1 and RAEB-2).

[e] Early-stage MDS includes untreated participants and participants in CR.

[f] Low-risk MDS refers to MDS ≤ 5% blasts (refractory anemia with or without ringed sideroblasts and refractory cytopenia with multilineage dysplasia).

Source: Adapted from Armand et al 2012 and Armand et al 2014.

Cytogenetic groups (Armand et al 2014):

For AML:

- AML favorable cytogenetics: t(8;21), inv(16), t(15,17)

  AML adverse cytogenetics: Complex karyotype (≥ 4 abnormalities)
- AML intermediate cytogenetics: All others

For MDS and AML arising from MDS:

- MDS adverse cytogenetics: Abnormal chromosome 7 or complex karyotype (≥ 4 abnormalities)
- MDS intermediate cytogenetics: All others

APPENDIX H. MANAGEMENT OF POTENTIAL HY'S LAW CASES/POTENTIAL DILI

INTRODUCTION

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential Hy's law criteria at any point during the study.

The investigator participates, in conjunction with Incyte clinical project and Pharmacovigilance representatives, in the review and assessment of cases fulfilling potential Hy's law criteria to ascertain whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug.

The investigator fulfills requirements for the recording of data pertaining to potential or Hy's law cases and AE/SAE reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

For the purpose of this process, definitions are as follows:

Potential Hy's law

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN at any point during the study. The elevations do not have to be at the same time or within a specified timeframe.

Hy's law

An increase in AST or ALT ≥ 3 × ULN and total bilirubin > 2 × ULN, where no other reason can be found to explain the combination of increases (eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug).

ACTIONS REQUIRED IN CASES OF AST OR ALT > 3 × ULN OR TOTAL BILIRUBIN > 2 × ULN

Identification and Determination of Potential Hy's Law

To identify cases of AST or ALT > 3 × ULN or total bilirubin > 2 × ULN and consequently determine whether the participant meets potential Hy's law criteria, please follow the instructions below:

- Review the laboratory report and if a participant has AST or ALT > 3 × ULN or total bilirubin > 2 × ULN at any visit:
  - Determine without delay whether the participant meets potential Hy's law criteria by reviewing laboratory reports from all previous visits.
  - Enter the laboratory data into the laboratory eCRF as soon as possible.

Potential Hy's Law Criteria Not Met

If the participant has **not** had AST or ALT ≥ 3 × ULN **and** total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Perform follow-up on subsequent laboratory results according to the guidance provided in Evaluation of Alternative Causes (below).

Potential Hy's Law Criteria Met

If the participant has had AST or ALT ≥ 3 × ULN **and** total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Have participant interrupt study drug.
- Notify Incyte study team without delay.
  - The investigator, or designee, should contact the medical monitor to discuss and agree upon an approach for the study participant's follow-up and the continuous review of data.
- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as medically indicated.
- Investigate the etiology of the event and perform any relevant diagnostic investigations as discussed with the medical monitor.
- Enter the laboratory data into the laboratory eCRF as soon as possible.
- If at any time (in consultation with the medical monitor) the potential Hy's law case meets serious criteria, report it as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality is initially detected and the criteria for potential Hy's law are met, the medical monitor, Incyte Pharmacovigilance physician, and investigator will discuss and review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug. Participant matter experts will be included in the review as appropriate.

Evaluation of Alternative Causes

In order to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, the following alternative etiologies should be considered, including but not limited to:

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis

- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if alkaline phosphatase is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment
- Other causes such as systemic infections (eg, bacterial, fungal, viral), nonalcoholic steatohepatitis, and cardiovascular diseases

Actions After Review and Assessment

According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the AST or ALT **and** total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the standard study processes.
- Have participant resume study drug as per Protocol guidelines.

If it is agreed that there is no explanation that would explain the AST or ALT and total bilirubin elevations:

- Have participant permanently discontinue study drug and perform end-of-treatment procedures.
- Report an SAE (report term "Hy's law").
  - The 'medically important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's law case, a causality assessment of related should be assigned.
- If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's law case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. Report an SAE (report term "Potential Hy's law") applying serious criteria and causality assessment as per above.

ACTIONS REQUIRED FOR REPEAT EPISODES OF AST OR ALT > 3 × ULN AND/OR TOTAL BILIRUBIN > 2 × ULN

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of potential Hy's law is based on the nature of the alternative cause identified for the previous occurrence.

If the alternative cause for the previous occurrence of potential Hy's law was not chronic or progressing malignant disease, please follow the process for potential Hy's law review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of potential Hy's law was chronic or progressing malignant disease, please follow the instructions below:

- Determine whether there has been a significant change* in the participant's condition.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described for potential Hy's law review and assessment as described in this appendix.

* A 'significant' change in the participant's condition refers to a clinically relevant change in ALT, AST, or total bilirubin, or associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

APPENDIX I. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	15 NOV 2024
Amendment 2	30 JAN 2026

Amendment 2 (30 JAN 2026)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to change the maximum duration of study drug administration [redacted]
Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4.1, Overall Design; Section 4.2, Overall Study Duration**

   Description of change: Deleted text regarding a maximum treatment duration of 2 years [redacted]

   Rationale for change: To align the Protocol with the current clinical development plan and to allow continued treatment for participants who derive ongoing clinical benefit from axatilimab [redacted]

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities; Table 4: Schedule of Laboratory Assessments)**

   Description of change: Added a footnote that for participants on a Q4W dosing schedule, the visit window is ± 7 days.

   Rationale for change: To allow flexibility in visit scheduling for participants who have derived clinical benefit and transitioned to a Q4W dosing schedule.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.10, Pulmonary Function Tests**

   Description of change: Clarified that for participants with documented lung involvement, PFTs should be performed at the same visit as cGVHD response determination and at the EOT visit.

   Rationale for change: Clarification.

4. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.3.8, Bone Turnover Markers; Section 8.4.1, Blood Sample Collection (Table 14: Pharmacokinetic and Antidrug Antibody Blood Sample Timing; Section 8.5, Pharmacodynamic and Translational Assessments (Table 15: Biomarker/Translational Sample Timing)**

   Description of change: Specified that samples for bone turnover markers, PK/ADA, and biomarkers will be collected for up to 2 years and that sample collection is not applicable at the EOT visit after 2 years.

   Rationale for change: To alleviate the burden on participants in regard to the change in the maximum treatment duration.

5. **Section 4.1, Overall Design; Section 4.2, Overall Study Duration**

   Description of change: Added that all participants who are receiving axatilimab at the time of marketing authorization in Japan will then discontinue study treatment and complete the EOT and safety follow-up visits.

   Rationale for change: To allow continued administration of axatilimab to participants who are deriving clinical benefit until a switch to the commercially available product is possible (ie, until regulatory approval is obtained).

6. **Section 6.1, Study Treatment Administered (Table 6: Study Treatment Information)**

   Description of change: Changed the upper limit of the administration time window to + 30 minutes and the upper limit of the infusion time to 60 minutes.

   Rationale for change: To align with the administration time in the ongoing axatilimab clinical studies and to reduce the complexity of dose administration.

7. **Section 6.6.1.2, Calcineurin Inhibitors and Mycophenolate Mofetil**

   Description of change: Added examples of substitutions of a CNI or an MMF.

   Rationale for change: Clarification.

8. **Section 6.7, Continued Access to Study Drug After the End of the Study**

   Description of change: Deleted text regarding completion of a 2-year treatment period, and added that participants may be prescribed the best standard of care available after completion of the study.

   Rationale for change: To align with the change in the maximum treatment duration.

9. **Appendix B, Required Laboratory Analysis**

   Description of change: Added a footnote note for HCV RNA that polymerase chain reaction is required and must be negative for HCV RNA in participants who are positive for HCV antibody.

   Rationale for change: Clarification.

10. **Incorporation of administrative changes.** Other regulatory guidance and administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1 (15 NOV 2024)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to provide clarity on the visit schedule at the time of a dose schedule change from Q2W to Q4W. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Added a note below the table that CxD1 is defined as the visit for study drug administration and to provide assessment directions for when the CxD1 dose is postponed.

   Rationale for change: To provide clarification of the scheduled dose day and assessments.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities; Table 4: Schedule of Laboratory Assessments); Section 6.5.1.5, Change to Dose Schedule for Axatilimab**

   Description of change: Added a footnote for Cycles 7+ Day 15 (± 3 days) that treatment assessment visits are not required for participants that change their dose schedule from Q2W to Q4W.

   Rationale for change: To clarify the visit schedule when the dose schedule is changed.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.11, Pulmonary Function Tests**

   Description of change: Added the EOT visit for PFT for participants with documented lung involvement.

   Rationale for change: To align with the NIH response for PFT assessment for participants with lung cGVHD.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.14, Chimerism and Graft Failure**

   Description of change: Added chimerism and graft failure assessment during treatment and follow-up period at EOT when investigator deems necessary.

   Rationale for change: To collect relevant data relating to late graft failure when applicable.

5. **Section 6.4, Stopping Rules and Dose Modifications**

   Description of change: Added dose adjustments to be recalculated if body weight increases or decreases more than 10% from baseline.

   Rationale for change: To provide clarification on the timing when recalculation of study drug is required.

6. **Section 6.5.1.3, Hematologic Toxicities: Dose Modification Guidelines for Axatilimab (Table 10: Hematologic Toxicities: Dose Modification Guidelines for Axatilimab)**

   Description of change: Changed the recovery period from 7 to 14 days to resume axatilimab at the next lower dose for the recurrence of the same hematologic toxicity.

   Rationale for change: To be consistent with dose discontinuation criteria.

7. **Section 6.5.1.4, Infusion-Related Reaction**

   Description of change: Added that premedication for IRR prophylaxis may be substituted for the site's standard regimen if the sponsor's medical monitor agrees.

   Rationale for change: To allow local standard and pediatric-specific prophylaxis regimens according to local institutional standards.

8. **Section 6.6.1.1, Corticosteroids; Section 6.6.1.2, Calcineurin Inhibitors and Mycophenolate Mofetil**

   Description of change: Added details that concomitant use of corticosteroids, CNI, and MMF must be reported in the specific eCRF page.

   Rationale for change: To provide clarification that concomitant corticosteroids, CNI, and MMF must be reported.

9. **Section 8.4.2, Immunogenicity Assessments; Section 8.6, Storage and Future Use of Biological Samples**

   Description of change: Included that the ADA, PK, biomarker, and PD samples will be stored for up to 10 years from the first CSR.

   Rationale for change: To be consistent with sponsor's sample storage rule.

10. **Section 8.5, Pharmacodynamic and Translational Assessments (Table 15: Biomarker/Translational Sample Timing)**

    Description of change: Added that the timing samples for serum biomarker and whole blood PBMC are to be collected at preinfusion and any time on Cycle 1 Day 8.

    Rationale for change: To clarify that additional samples can be collected any time on Cycle 1 Day 8.

11. **Appendix B, Required Laboratory Analytes**

    Description of change: Added direct and indirect bilirubin for blood chemistries to the table.

    Rationale for change: To clarify both items are required when total bilirubin is elevated.

12. **Appendix E, Global Chronic GVHD Activity Assessment (Clinician Report)**

    Description of change: Included a list of areas in the cGVHD activity assessment (Form A) that are to be performed when clinically necessary.

    Rationale for change: These data will not be captured in database.

13. **Incorporation of administrative changes.** Other administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Signature Page for VV-CLIN-025864 v3.0

Approval Task	[redacted] Document Preparer [redacted] Biostatistics 30-Jan-2026 18:35:58 GMT+0000
Approval Task	[redacted] Approver [redacted]Clinical Development 30-Jan-2026 18:54:07 GMT+0000
Approval Task	[redacted] Approver [redacted]of Development, Japan 30-Jan-2026 21:31:59 GMT+0000
Approval Task	[redacted] Document Preparer [redacted] Clinical Research Scientist 01-Feb-2026 11:55:25 GMT+0000
Approval Task	[redacted] Document Preparer [redacted] & Risk Management 02-Feb-2026 03:35:13 GMT+0000
Approval Task	[redacted] Approver [redacted]of Development Operations Japan 02-Feb-2026 07:24:08 GMT+0000

Signature Page for VV-CLIN-025864 v3.0