CLINICAL STUDY PROTOCOL

Protocol Title:	AGAVE-201, A Phase 2, Open-label, Randomized, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of Axatilimab at 3 Different Doses in Patients with Recurrent or Refractory Active Chronic Graft Versus Host Disease who have Received at least 2 Lines of Systemic Therapy
Protocol Number:	SNDX-6352-0504
Protocol Amendment	4.0 GLOBAL
Study Intervention:	Axatilimab (SNDX-6352)
Study Phase:	Phase 2
Sponsor Name:	Syndax Pharmaceuticals, Inc.
Legal Registered Address:	35 Gatehouse Drive Building D, Floor 3 Waltham, MA 02451
Regulatory Agency Identifier Number(s):	IND: 139,019
Protocol Date:	Version 5.0, 05 April 2023 GLOBAL

SPONSOR SIGNATORY

[redacted]

[redacted]

Date

[redacted]

INVESTIGATOR'S AGREEMENT

I have read the attached protocol (SNDX-6352-0504) entitled "AGAVE-201, A Phase 2, Open-label, Randomized, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of Axatilimab at 3 Different Doses in Patients with Recurrent or Refractory Active Chronic Graft Versus Host Disease who have Received at least 2 Lines of Systemic Therapy," dated 05 April 2023 version 5.0 GLOBAL, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation Tripartite E6 Guideline on Good Clinical Practice applicable regulations of the Food and Drug Administration and other applicable regulations.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me
- my sub-investigators

at the start of the study, at study completion, and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Syndax.

_____

Signature

_____ _____

Name of Principal Investigator Date

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol V5.0, Amendment 4.0 (GLOBAL)	05 April 2023
Protocol V4.0, Amendment 3.0 (GLOBAL)	24 May 2022
Protocol V3.0, Amendment 2.0 (GLOBAL)	17 December 2020
Protocol V2.0, Amendment 1.0	23 November 2020
Original Protocol V1.0	17 September 2020

Amendment: Amendment 3.0 (Version 4.0) dated 24 May 2022 has been updated to Amendment 4.0 (Version 5.0) GLOBAL dated 05 April 2023.

Overall Rationale for the Amendment: The reasons to amend Protocol SNDX-6352-0504, from Protocol Amendment 3.0 (GLOBAL) to Protocol Amendment 4.0 (GLOBAL), are detailed below. Minor editorial changes, including changes for consistency, for example, to the list of abbreviations, have not been listed here. For full details, please refer to the red-line version of the protocol.

Amendment 4.0 Summary of Changes		
Section	**Description of Change**	**Rationale**
Section 1.1: Overall Design; And Section 4.1: Overall Study Design	Added additional description of analysis plan for futility, interim analysis (IA) #1 and IA #2, and safety assessment to explain considerations for Independent Data Monitoring Committee (IDMC) review. Details on the final efficacy and safety analyses were added.	Based on IDMC recommendations and subsequent advice from the US Food and Drug Agency regarding dose, updates were incorporated into the protocol. Originally IA #2 was designed as a second futility analysis of the Stage 1 patients in each cohort after a longer treatment interval. However, given the fact that the study is fully enrolled, this analysis would be too limited to accurately assess the benefit/risk of proceeding with the protocol at the time of IA #2.
Section 1.1: Dosing Arms and Duration of Treatment; And Section 4.4: End of Study Definition	Table revised to include guidance on patients who derive benefit after 2 years and to include Overall Survival follow-up period and End of Study.	To further clarify Overall Survival stage of the study.
Section 1.3: Schedule of Activities (SoA)	Table revised to add SoA for Overall Survival follow-up and Cycles 25+. Abbreviations and footnotes were also updated to reflect changes in the table.	Additional visits were included to accommodate patients who may continue to receive axatilimab if deriving benefit per the Investigator and Syndax post 2 years of treatment.
Section 2.3: Benefit and Risk Analysis	Last sentence of Paragraph 4 was modified to, "The study design aims to provide patients with maximal benefit from axatilimab and reduced unnecessary risk, by monitoring all potential risks, and incorporating early stopping rules for futility and safety," which removed mention of intrapatient dose escalation.	Based on IDMC recommendations and subsequent advice from the US Food and Drug Agency regarding dose, updates were incorporated into the protocol.

Amendment 4.0 Summary of Changes		
Section	**Description of Change**	**Rationale**
Section 3: Objectives and Endpoints and Section 9.4.1 Efficacy Analysis	Updated Key Secondary Endpoint: Proportion of patients with a ~~>5-point~~ clinically significant improvement in modified Lee Symptom Scale score (mLSS).	Based on advice from the US Food and Drug Agency.
Section 3: Objectives and Endpoints and Section 9.4.1 Efficacy Analysis	Added an Exploratory Efficacy Endpoint: Duration of improvement of mLSS for patients with ≥7 point improvement.	Based on advice from the US Food and Drug Agency.
Section 6.2: Intrapatient Dose Escalation	Revised to read: "Intrapatient dose escalation is not permitted. Dose adjustment(s) related to change in dosing schedule (Section 6.3.) are not considered dose escalations as the dose intensity remains unchanged."	Based on IDMC recommendations and subsequent advice from the US Food and Drug Agency regarding dose, updates were incorporated into the protocol.
Section 6.2.1: Dose Changes Following IDMC Recommendations	Section revised to provide additional guidance on changes to dosing following IDMC recommendations and regulatory agency interactions. Main changes included: patients randomized to 3 mg/kg Q4W must reduce dose to 0.6 mg/kg Q4W; patients randomized at 1 mg/kg Q2W may continue at their current dose, or transition to 0.3 mg/kg Q2W; patients randomized at 0.3 mg/kg Q2W may continue at their current dose; and patients who have had their dosing schedule adjusted per Section 6.3 must reduce their dose to 0.6 mg/kg Q4W, if they continue treatment on a Q4W schedule, or revert to the Q2W schedule at a dose used immediately prior to schedule adjustment.	Based on IDMC recommendations and subsequent advice from the US Food and Drug Agency regarding dose, updates were incorporated into the protocol.
Section 6.3: Changes to Dosing Schedule	Section and all subsections revised to note that the highest dose available after any change would be 0.6 mg/kg Q4W.	Based on IDMC recommendations and subsequent advice from the US Food and Drug Agency regarding dose, updates were incorporated into the protocol.
Section 6.7: Stopping Rules and Dose Modifications	Table 4 and its footnotes were revised to reflect new dose levels after 11 November 2022 of 0.6 mg/kg IV Q4W and 0.3 mg/kg IV Q2W.	Based on IDMC recommendations and subsequent advice from the US Food and Drug Agency regarding dose, updates were incorporated into the protocol.
Section 6.7.2: Discontinuation of Study Treatment for Lack of Efficacy	Definition of unequivocal progression of chronic graft-versus-host disease (cGVHD) added as "initiation of new systemic therapy for cGVHD; increase in corticosteroid and/or CNI/mTOR inhibitor dose beyond those allowed by protocol."	To clarify definition of unequivocal progression of cGVHD.
Section 8.3.1: Time Period and Frequency for Collecting AE and SAE Information	Reporting timelines to the Sponsor were added for the adverse events of special interest (AESIs) of infusion-related reactions (IRRs) and infections.	24-hour reporting window for nonserious infections has been removed because of clinical experience on the axatilimab protocols to date. Infectious AESIs are entered regularly in the EDC and monitored in safety reviews.
Section 9.2: Sample Size Determination	Details on the final efficacy and safety analyses were added.	Based on actual study conduct and observed over-enrollment.
Section 9.4.5: Interim Analysis	Table 12 (Toxicity Stopping Boundaries) revised to specify stopping boundaries for IA #1. Section revised to include details on the analysis plan for IA #1, IA #2, and Final Analysis. Additions included	Based on IDMC recommendations and subsequent advice from the US Food and Drug Agency regarding dose, updates were incorporated into the protocol.

Amendment 4.0 Summary of Changes		
Section	**Description of Change**	**Rationale**
	those on the futility assessments, overall evaluation of clinical data, and safety assessment.	Originally IA #2 was designed as a second futility analysis of the Stage 1 patients in each cohort after a longer treatment interval. However, given the pace of enrollment, this analysis would be too limited to accurately assess the benefit/risk of proceeding with the protocol.
Section 10.3.6: Reporting of SAEs and AESI	Text clarifying type of AESI added reading: "infusion-related reactions, including hypersensitivity reactions."	To provide clarity on why infectious AESIs are not being reported in an expedited fashion.
Section 11: References	Missing references added.	Add additional references

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

AGAVE-201, A Phase 2, Open-label, Randomized, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of Axatilimab at 3 Different Doses in Patients with Recurrent or Refractory Active Chronic Graft Versus Host Disease who have Received at least 2 Lines of Systemic Therapy.

Short Title:

Phase 2 Study of Axatilimab at 3 Different Doses in Patients with Chronic Graft Versus Host Disease.

Rationale:

Chronic graft-versus-host disease (cGVHD) remains the major cause of morbidity and non-relapse mortality after allogeneic hematopoietic stem cell transplantation (HSCT). cGVHD typically manifests with multiorgan pathology which often occurs during the first-year post-HSCT but can also develop beyond the first year post-HSCT (Jagasia 2015).

Treatment of cGVHD is currently based on steroid administration and although many other approaches, including additional immune suppressants, ultraviolet B (UVB) phototherapy, and extracorporeal photopheresis (ECP) are commonly used, none have proven clearly effective. Targeting pathogenic monocyte derived macrophages by preventing their differentiation and survival through the inhibition of colony stimulating factor 1 receptor (CSF-1R) has proven highly effective in animal systems.

Axatilimab is a humanized IgG4 monoclonal antibody (mAb) directed against CSF-1R with the potential to treat cGVHD through blockade of macrophage activity.

Data from the current axatilimab Phase 1/2 study in patients with cGVHD (SNDX-6352-0503) demonstrate that axatilimab is biologically and clinically active, inducing organ specific responses and symptom improvement, with no significant adverse events. These data support evaluation of axatilimab as described in the proposed registration enabling Phase 2 study, SNDX-6352-0504.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the overall response rate (ORR) of axatilimab at 0.3 mg/kg IV Q2W, 1 mg/kg IV Q2W, and 3 mg/kg IV Q4W in patients with cGVHD after failure of least 2 prior lines of therapy.	• ORR in the first 6 cycles as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD.
Key Secondary - Efficacy	
• To evaluate key secondary measures of clinical benefit	• Proportion of patients with a clinically significant improvement in modified Lee Symptom Scale score (mLSS).
Secondary - Efficacy	
• To evaluate secondary measures of clinical benefit.	• ORR on study as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD. • Duration of Response (DOR) defined as the time from initial response of PR or CR until documented progression of cGVHD, start of new therapy, or death for any reason. • Sustained response rate (SRR) • Organ-specific response rate based on 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD • Joints and fascia response rate based on refined NIH response algorithm for cGVHD (Inamoto 2020) • Percent reduction in average daily dose (or equivalent) of corticosteroids • Proportion of patients who discontinue corticosteroid use after study entry. • Percent reduction in average daily dose (or equivalent) of calcineurin inhibitors • Proportion of patients who discontinue calcineurin inhibitors use after study entry

Objectives	Endpoints
Secondary – Safety	
• To evaluate the safety and tolerability of axatilimab in patients with cGVHD	• Frequency and severity of adverse events (AEs) and serious adverse events (SAEs) • Change from baseline in values for vital signs, safety laboratory parameters, physical and neurological examination, electrocardiogram (ECG) and Karnofsky/Lansky performance scale
[redacted]	
Secondary - PK/Pharmacodynamic	
• To assess the plasma population PK (pop PK) profile of axatilimab in patients with cGVHD	• Axatilimab PK parameters and patient factors that may explain variability in drug exposure
• To assess pharmacodynamic profile of axatilimab	• Change from baseline in colony stimulating factor 1 (CSF-1), interleukin 34 (IL-34) levels and its association with cGVHD response
• To determine or assess the changes in monocyte level with response	• Change from baseline in circulating monocyte number and phenotype (CD14/16)
• To determine or assess the baseline in monocyte level with response	• Baseline circulating monocyte number and phenotype (CD14/16)
Secondary – Immunogenicity	
[redacted]	
[redacted]	

Objectives	Endpoints
	[redacted]
Exploratory – Efficacy	
• To explore possible additional evidence of clinical benefit.	[redacted] • Proportion of patients with Failure Free Survival (FFS) at Cycle 7 Day 1 and 1 year. FFS is defined as the time from randomization to addition of another systemic immune suppressive therapy for cGVHD, relapse of underlying malignancy, or death whichever is earlier. • Overall survival (OS) • Time to response [redacted]

Overall Design:

AGAVE-201 is a Phase 2, open-label, randomized, multicenter study to evaluate the efficacy, safety and tolerability of axatilimab at 3 different dose levels, in patients with recurrent or refractory active cGVHD who have received at least 2 prior lines of systemic therapy due to progression of disease, intolerability or toxicity. Disease progression is defined 1) by the NIH 2014 consensus criteria, either in terms of organ specific algorithm or global assessment or, 2) as active, symptomatic cGVHD for whom the physician believes that a new line of systemic therapy is required.

The study will consist of 3 periods: Screening, Treatment, and Follow-up. Throughout the study, patients will be evaluated as specified in the Schedule of Activities (SoA) (Section 1.2).

After signing informed consent, potential candidates will undergo screening procedures to determine eligibility. At enrollment, eligible patients will be randomized to one of 3 dose cohorts (axatilimab 0.3 mg/kg IV every 2 weeks [Q2W], 1 mg/kg IV Q2W, or 3 mg/kg IV Q4W). Patients must begin treatment (Cycle 1 Day 1) within 3 days of randomization/enrollment and will receive axatilimab from Cycle 1 Day 1, in 4-week (28-day) treatment cycles, until disease progression (as defined by the NIH 2014 consensus criteria), lack of efficacy by 9 months (Section 6.7.2), withdrawal of consent, or unacceptable toxicity. Following treatment discontinuation, patients will receive an End of Treatment (EOT) visit 30 days after the last dose of study drug.

Simon's optimal 2-stage design will be implemented within each dose cohort. In the first stage 27 patients will be randomized to each of the 3 dose cohorts. To limit the potential exposure of patients to an inefficacious dose and obviate the need for a pause in accrual, the initial futility analysis will be based on an early endpoint (ie, overall response in the first 3 cycles). Each dose will be evaluated for futility and unacceptable toxicity as follows:

- Interim Analysis (IA) #1: Futility assessment based on responses in the first 3 cycleswill be conducted. This assessment will occur when the first 27 patients in each cohort have had the opportunity to complete 3 cycles of therapy. If ≤6 patients achieve a response after the first 3 cycles of axatilimab (up to and including cycle 4, day 1 assessment), the randomization to this dose level may be stopped for futility. Safety assessment will occur at this IA. For IA # 1, the boundary for unacceptable toxicity is ≥8 out of the first 27 patients having a toxic event defined as any serious or severe (≥Grade 3) TEAE that is attributed to study drug. Grade 2 events that are considered treatment-related and result in medical intervention or hospitalization will be counted as a toxic event.
- IA #2: IA #2 will consist of an overall evaluation of available clinical data. It will be conducted when the first 27 patients in each cohort have had the opportunity to complete 6 cycles of therapy. If ≤9 patients achieve a response to axatilimab, the randomization to this dose level will be stopped for futility. For IA#2, given the full enrollment of the study as of this amendment, the rate of toxicity events will be provided for all treated patients and will be reviewed as part of the overall benefit/risk assessment. For the overall benefit/risk assessment, a comprehensive safety and efficacy analysis will be provided to the IDMC:
  - Safety for all participants.
  - Efficacy for all participants who have had the opportunity to receive 3 cycles of axatilimab.

Study randomization will not pause while data from the interim analyses are being evaluated.

An Independent Data Monitoring Committee will evaluate all data that are available at the time of the data cut for the interim analyses, and provide a recommendation on continued use of the available axatilimab dose levels.

A final efficacy analysis will be performed when all patients have had the opportunity to complete 6 cycles of treatment with axatilimab. A dose level will be considered successful if ≥29 patients have had a response to axatilimab (PR or CR), as defined by NIH 2014 cGVHD criteria. The final boundary for efficacy will be re-calculated if there is over enrollment in the second stage of the design. For example, if the total number of randomized patients in a dose level is 80, this dose level will be considered successful if ≥32 patients have had a response to axatilimab.

At the final analysis, if 19 or more patients out of the total 70 patients experience a toxic event (the boundary will be re-calculated if there is over enrollment), this will indicate a 90% posterior probability of the toxicity rate exceeding 20% but the final determination of acceptability of a given dose will be based on the overall benefit/risk indicated by review of the totality of evidence.

Patients enrolled into a Q2W regimen may be eligible to change to a Q4W dosing during the study, as described in Section 6.3. Additional dosing modifications for already enrolled patients may be implemented following IDMC recommendation on closing enrollment to one or more dose level cohorts and are specified in Section 6.2.1.

The on-treatment response criteria will be assessed every 4 weeks and at the EOT visit or discontinuation of the study intervention using 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD: CR, PR, lack of response (unchanged, mixed or progression).

Disclosure Statement:

- Stage 1 is to evaluate each dose regimen for efficacy and safety; with futility IA.
- Stage 2 is to evaluate the efficacy and safety of axatilimab at the selected dose(s).

Number of Patients:

- In Stage 1, 27 patients will be enrolled into each treatment arm (0.3 mg/kg IV Q2W, 1 mg/kg IV Q2W, and 3 mg/kg IV Q4W).
- In Stage 2, an additional 43 patients will be enrolled into each of the treatment arms which have passed the futility and safety evaluations from Stage 1.

Dosing Arms and Duration of Treatment:

There will be 3 dosing arms: 0.3 mg/kg IV Q2W, 1 mg/kg IV Q2W, and 3 mg/kg IV Q4W. Total study duration for each patient will be up to 28 months as follows:

Screening period:	Up to 28 days (1 month) prior to the first dose of study intervention
Treatment period:	Until unequivocal disease progression or unacceptable toxicity up to a maximum period of 2 years. Patients who continue to derive benefit after 2 years of treatment, administration may continue following consultation with sponsor.
Safety Follow-up period:	Up to 90 days (3 months) after the last administration of study intervention
Overall Survival Follow-up period:	After completing safety follow-up, patients will be contacted every 3 months to assess overall survival for up to 5 years.
End of Study	The final contact with the last patient for survival follow-up.

Dosing Methods:

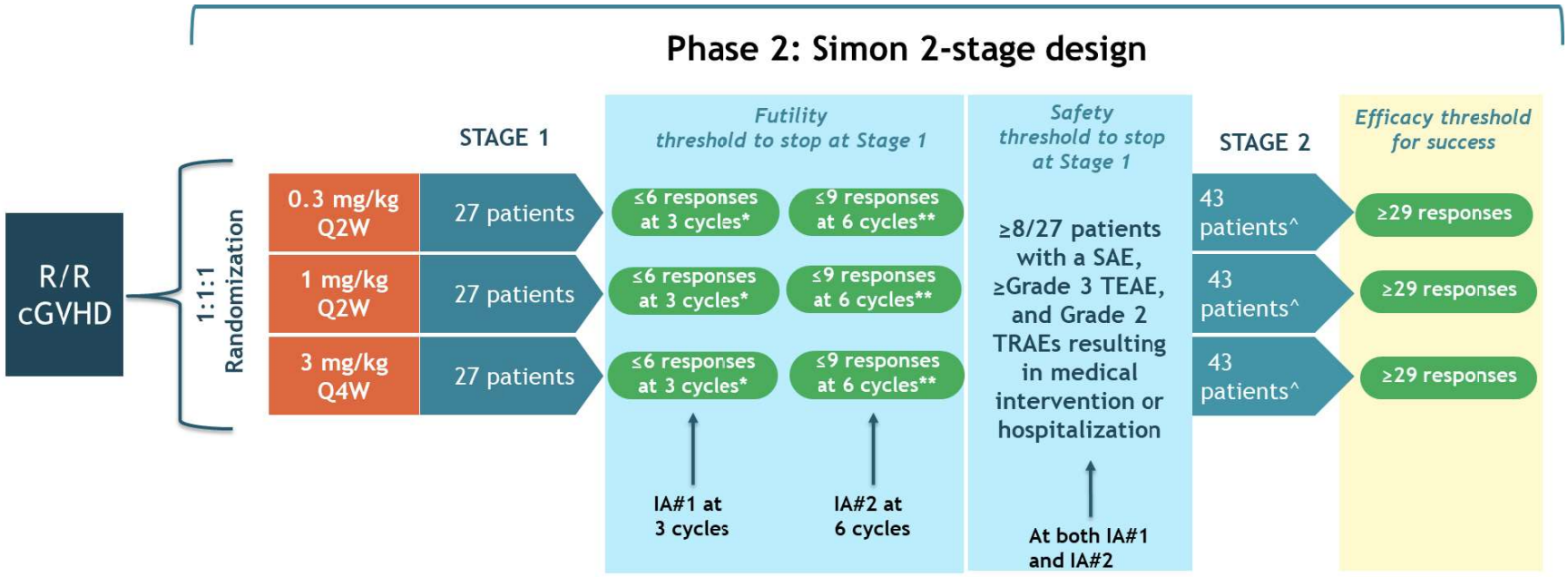
Patients will receive axatilimab IV at a dose and regimen according to the dosing cohort that they are randomized to as follows:

- 0.3 mg/kg IV Q2W

- 1 mg/kg IV Q2W
- 3 mg/kg IV Q4W

Independent Data Monitoring Committee: Yes

1.2. Study Schema



* Efficacy assessment at 3 cycles
**Efficacy assessment at 6 cycles
^ All patients enrolled at the selected dose(s) will be evaluated for efficacy

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities

Study Procedure	Screening	Treatment Period								Safety Follow-Up			OS Follow-Up
		Cycle (each cycle consists of 28-days)											
		Cycle 1				Cycles 2 to 6		Cycle 7-24[1]	Cycle 25+	Days post last dose ±7 days			Up to 5 years after Cycle 1 day 1
Day in Cycle	-28 to 0	1	8	15	22	1	15	1/15	1/15	+30[2] (EOT)	+60	+90	Every 3 months
Visit Window	NA	NA	±1D	±1D	±1D	±3D	±3D	±3D	±3D	±7D	±7D	±7D	±15D
Informed consent	X												
Demographics[3]	X												
Eligibility criteria	X												
Medical & disease history[4] & prior medications	X												
Karnofsky/Lansky Performance Scale	X	X				X		X[5]		X	X	X	
Complete physical examination	X	X[6]								X	X	X	
Height	X												
Randomization[7]	X												
[redacted]													
Symptoms-directed physical exam			X	X	X	X	X	X	X				
Vital signs[9] and weight	X	X	X	X	X	X	X	X	X	X	X	X	

Study Procedure	Screening	Treatment Period								Safety Follow-Up			OS Follow-Up
		Cycle (each cycle consists of 28-days)											
		Cycle 1				Cycles 2 to 6		Cycle 7-24[1]	Cycle 25+	Days post last dose ±7 days			Up to 5 years after Cycle 1 day 1
Day in Cycle	**-28 to 0**	**1**	**8**	**15**	**22**	**1**	**15**	**1/15**	**1/15**	**+30[2] (EOT)**	**+60**	**+90**	**Every 3 months**
Visit Window	**NA**	**NA**	**±1D**	**±1D**	**±1D**	**±3D**	**±3D**	**±3D**	**±3D**	**±7D**	**±7D**	**±7D**	**±15D**
Neurological examination	X	X				X		X[5]		X	X	X	
12-Lead Electrocardiogram	X	As clinically indicated								X			
Pulmonary Function Tests[10]	X					X		X[10]					
Safety Laboratory (hematology, & biochemistry)[11]	X	X	X	X	X	X	X	X[12]	X[12]	X	X		
Coagulation factors	X					X[13]							
[redacted]													
HCV RNA[15]	X												
HBV[16]	X												
TB[17]	X												
Urinalysis	X		As clinically indicated							X			
Pregnancy testing[18]	X	X[19]				X[19]		X[19]	X[19]	X[18]			
Axatilimab administration		X		X[20]		X	X[20]	X[20]	X[20]				
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	

Study Procedure	Screening	Treatment Period								Safety Follow-Up			OS Follow-Up
		Cycle (each cycle consists of 28-days)											
		Cycle 1				Cycles 2 to 6		Cycle 7-24[1]	Cycle 25+	Days post last dose ±7 days			Up to 5 years after Cycle 1 day 1
Day in Cycle	**-28 to 0**	**1**	**8**	**15**	**22**	**1**	**15**	**1/15**	**1/15**	**+30[2] (EOT)**	**+60**	**+90**	**Every 3 months**
Visit Window	**NA**	**NA**	**±1D**	**±1D**	**±1D**	**±3D**	**±3D**	**±3D**	**±3D**	**±7D**	**±7D**	**±7D**	**±15D**
[redacted]													
Physician-reported cGVHD global activity assessment[21, 22]		X				X		X[23]		X			
Patient cGVHD Self-Assessment (mLSS)		X				X		X[23]		X			
Pharmacokinetics		See Table 2 for collection times											
Pharmacodynamics		See Table 2 for collection times											
[redacted]													
Tissue biopsy[25]	X					X[26]							
Overall survival													X[27]

Abbreviations: [redacted] HBV = hepatitis B virus; HCV RNA = hepatitis C virus ribonucleic acid; mLSS = modified Lee Symptom Scale; TB = tuberculosis

1. Patients who meet the criteria detailed in Section 6.3 may change their dosing schedule. The Day 15 visit is only applicable for patients on a Q2W regimen.
2. In case of early discontinuation, this visit (30 days after last dose of study intervention) will serve as end of study visit.
3. Includes age, race, and ethnicity.
4. A complete medical history will be documented and updated prior to the administration of the first dose of study intervention. The medical history will include cancer history, including date of and stage at diagnosis, method of diagnosis, all previous treatments and response to such treatment, and any medical condition that might complicate the patient's disease or affect the treatment outcome.
5. Assessment to be performed on Day 1 of each cycle.
6. If the Screening complete physical exam was performed within 7 days before C1D1, a symptom-directed physical exam may be performed at randomization.
7. Patients must be randomized within 3 days prior to C1D1.

[redacted]

9. Vital signs should be performed before every infusion. In addition, for the first 2 infusions, they should also be performed during and after the infusion. Thereafter (from the third infusion on), they should be performed during or after the infusion, if clinically indicated.
10. Age-appropriate Pulmonary Function Tests (PFTs) performed within 4 weeks prior to the scheduled first dose for all patients. For patients with documented lung involvement, frequency beyond C1 will be every 3 cycles (±7 days) up to and including C24.
11. For all patients, labs should be taken at each visit in Cycle 1, for Cycle 1 Day 1 labs may be drawn up to 2 days prior to dosing. From Cycle 2 on, labs should be taken up to 2 days prior to each dose but within the visit window. In Cycle 2 for patients on the Q4W regimen, labs do not need to be drawn on Day 15 of each cycle. Refer to Appendix 2 (Section 10.1) for full list of clinical laboratory tests. Maximum daily blood draw from a patient weighing 41-45 kg (equating to a patient of approximately 12 years of age) is 160 mL (5% blood volume) and maximum blood draw over 8 weeks is 320 mL (10% blood volume). When adding up all blood draws, including those detailed in Table 1/Table 2, the maximum blood volume to be drawn on any one day will be 63.5 mL and the total blood to be drawn over the first 60 days (through Cycle 3 Day 1) will be 284.5 mL. If urea level is reported by the local site laboratory instead of blood urea nitrogen (BUN), BUN level should be calculated formulas detailed in Section 10.2 and entered in the appropriate field in the eCRF.
12. Labs should only be taken on Day 15 of each cycle if clinically indicated.
13. On Cycle 3 Day 1 only, if the patient is having a skin biopsy, the coagulation sample should be collected first (ie, before the skin biopsy).
14. To be collected on C1D1, C3D1, C6D1, C12D1 and EOT, samples should be collected pre-dose.
15. Polymerase chain reaction is required and must be negative for HCV RNA in patients positive for HCV antibody.
16. Hepatitis B screening: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, immunoglobulin G and M.
17. Evidence of negative QuantiFERON test within 28 days prior to the first dose of axatilimab.
18. For female patients of child-bearing potential, a serum pregnancy test is required to be performed during screening and within 3 days before the first study intervention dose if the screening pregnancy test is performed more than 3 days before the first study intervention dose. A serum pregnancy is also required at the end of study. During the study, either urine or serum pregnancy tests are performed.
19. Pregnancy testing is to be repeated every 4 weeks from Cycle 1 Day 1.
20. Patients receiving axatilimab on a Q4W regimen will only be administered study drug on Day 1 of each cycle (not on Day 15).
21. Response evaluation will be according to 2014 NIH Consensus definitions; Window periods of ±3 days will be allowed for each response assessment (unless otherwise specified).
22. It is preferred that all cGVHD assessments be done by the same health care provider who completed the C1D1 assessment. At minimum, the C7D1 assessment should be performed by the same health care provider who performed the C1D1 assessment. In addition, any assessments leading to changes in cGVHD therapy must be confirmed by the PI or primary treating physician.
23. Assessments should be made D1 of each cycle C7-C12 inclusive. Cycle 13-24 assessments should be made every 12 weeks.

[redacted]

25. Optional skin biopsy only in patients with skin cGVHD; optional lung biopsy only in patients with transbronchial lung cGVHD.
26. Optional biopsy will be done on C3D1.
27. After completing safety follow-up, patients will be contacted every 3 months to assess for any long-term safety signal such as secondary malignancies or chronic infection and overall survival for up to 5 years.

Table 2 PK Collection Schedule

	C1								C2		C3	C4		C5 to C12
	Day 1		Day 8		Day 15		Day 22[1]		Day 1		Day 1	Day 1		Day 1
Sample	**PK**	**PD**	**PK**	**PD**	**PK[2]**	**PD**	**PK**	**PD**	**PK**	**PD**	**PK**	**PK**	**PD**	**PK**
Predose[3]	X	X	X[4]	X	X	X	X	X	X	X	X	X	**X**	X
30 min (immediately after the end of infusion) (+5 min)	X				X							X		
1 hour (after infusion start) (±5 min)	X				X							X		
6 hours (after infusion start) (±10 min)	X				X							X		
Total blood volume (mL)[5]	24	22	6	22	24	22	6	3	6	22	6	24	**22**	6

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics

1. For patients on a Q4W regimen.
2. A single PK sample should be collected on Day 15 for patients on a Q4W regimen.
3. On days patients receive an SNDX-6352 dose samples will be collected pre-dose.
4. This sample may be taken ±24 hours.
5. Maximum daily blood draw from a patient weighing 41-45 kg (equating to a patient of approximately 12 years of age) is 160 mL (5% blood volume) and maximum blood draw over 8 weeks is 320 mL (10% blood volume). When adding up all blood draws, including those detailed in Table 1/Table 2, the maximum blood volume to be drawn on any one day will be 63.5 mL and the total blood to be drawn over the first 60 days (through Cycle 3 Day 1) will be 284.5 mL.

2. INTRODUCTION

2.1. Study Rationale and Hypothesis

Chronic graft versus host disease (cGVHD) remains the major cause of morbidity and non-relapse mortality after allogeneic hematopoietic stem cell transplantation (HSCT). cGVHD typically manifests with multiorgan pathology which often occurs during the first-year post-HSCT but can also develop beyond the first year post-HSCT (Jagasia 2015). Treatment of cGVHD is currently based on steroid administration. While progress has been made with improvements in survival outcomes over time, current available therapies are associated with significant toxicities, and many currently available salvage therapies are associated with increased immunosuppression, infectious complications, and potential loss of the graft versus leukemia (GVL) effect. Thus, there is an unmet need for development of newer treatment strategies for cGVHD to improve long-term post-transplant outcomes and quality of life for HSCT recipients (Hill 2018).

Based on nonclinical pharmacology studies in mouse models of interleukin (IL)-17 dependent skin and lung GVHD it was demonstrated that targeting CSF-1/CSF-1R signaling pathway prevents and treats cGVHD through depletion of donor-derived macrophages (Alexander 2014). These studies established that donor bone marrow derived macrophages were responsible for generating the fibrotic disease symptoms of cGVHD and that with blockade of colony stimulating factor 1 (CSF-1) dependent monocyte recruitment, differentiation and proliferation ameliorated and prevented the development of cGVHD. In these nonclinical models, depletion of macrophages using an anti-CSF-1R mAb markedly reduced cutaneous and pulmonary cGVHD. Taken together, these data support a key role for donor-derived macrophages in the development of cGVHD and suggest that targeting CSF-1 signaling after transplantation may prevent and treat cGVHD (reviewed in MacDonald, 2017).

Axatilimab is a humanized IgG4 monoclonal antibody (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 two known ligands, colony stimulating factor-1 (CSF-1) and interleukin-34 (IL-34).

Currently, axatilimab is being evaluated in a Phase 1/2 study in patients with cGVHD who have received at least two lines of prior therapy (SNDX-6352-0504). A summary of the study including preliminary safety, pharmacokinetic (PK), pharmacodynamic, and clinical response data is provided in Section 2.2.1. [redacted]

These data support evaluation of axatilimab as described in the proposed registration enabling Phase 2 study, SNDX-6352-0504; a study evaluating the efficacy, safety, and tolerability of axatilimab in patients with cGVHD who have failed ≥2 prior lines of systemic therapy due to progression of disease, intolerability or toxicity.

2.2. Background

cGVHD is an immune-mediated serious and life-threatening complication after allogeneic HSCT, occurring in 30% to 70% of patients (Jagasia 2015, Merkel 2016). The prevalence and severity of cGVHD have increased during the past 2 decades in association with the increasing use of hematopoietic HSCT, the widespread use of mobilized blood cells instead of marrow for grafting, and improvements in survival during the first several months after allogeneic HSCT (Flowers and Martin 2015).

The disease has a wide range of pleomorphic manifestations, and many 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 linger for years. Manifestations of chronic GVHD can resemble autoimmune or other immune-mediated disorders such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency. cGVHD generally involves several organs or sites, patients frequently have erythematous rash, enteritis, or hepatic involvement characterized by transaminase elevation or hyperbilirubinemia at initial presentation and intermittently afterward 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 >1 year from HSCT occurs in <10% of cases (Flowers and Martin 2015).

The 2005 National Institutes of Health (NIH) Consensus Conference developed a framework for characterizing the pleomorphic manifestations of chronic GVHD. The consensus project defined minimal criteria for the clinical diagnosis, established criteria for scoring the severity of clinical manifestations in affected organs and proposed new categories for describing overall disease severity and indications for treatment. The consensus project also proposed measures for monitoring disease progression and response to therapy. It provided guidance for clinical trials to support bringing forward therapies that will provide a durable meaningful difference to patients' clinical symptoms and quality of life. In 2014, the NIH Conference was reconvened and the proposed revisions, based on ongoing clinical evaluation of the disease, were incorporated. The NIH guidance has been supported by the US Food and Drug Administration (FDA) as an appropriate means to measure disease and response to therapy.

While the pathophysiological understanding of cGVHD is emerging, there has been little meaningful development of therapies for patients with cGVHD. Currently, there remains a long-standing reliance on prednisone as the mainstay of 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 2017). An effort to decrease corticosteroid doses has led to their use in combination with other immunosuppressants, such as cyclosporine, tacrolimus, and sirolimus, in frontline or second-line settings, despite a lack of clinical evidence supporting additional efficacy after combining these agents with corticosteroids (Miklos 2017).

Approximately 50% to 60% of patients with cGVHD require secondary treatment within 2 years after initial systemic treatment. Despite no consensus with respect to optimal choice of agent, they have typically included rituximab or imatinib (Flowers and Martin 2015). In 2017 Imbruvica® (ibrutinib), a BTK inhibitor, became the first FDA approved therapy for the

treatment of adult patients with cGVHD, indicated for patients who have received ≥1 lines of therapy. The side effects of ibrutinib are significant with 38% of patients discontinuing due to an adverse event and 31% of patients dose reducing in the pivotal evaluation of ibrutinib in patients with cGVHD. Additionally, investigators have noted that they do not give ibrutinib to a large proportion of their cGVHD patients due to the organ system involvement of the patients that participated in the clinical development program.

Based on recent insights into the molecular mechanisms involved in the disease-related inflammatory process, interventions targeting kinases involved in signaling pathways such as BTK, JAK1/2, Syk, and ROCK2 have been investigated and have shown promising results in nonclinical and patient sample correlative studies (MacDonald 2017); BTK and ROCK2 inhibition have shown evidence of efficacy in Phase 1/2 clinical studies (Miklos 2017).

[redacted]

2.2.1. Clinical Experience with Axatilimab in Patients with cGVHD

SNDX-6352-0503 is a Phase 1 dose-finding and Phase 2 dose-expansion study evaluating the safety, tolerability, PK/pharmacodynamic, and efficacy of axatilimab in patients with active cGVHD whose disease has progressed after having received at least 2 prior lines of therapy. As of 22 October 2021, 40 patients had received at least 1 dose of study drug: 17 patients in the Phase 1 dose-escalation portion and 23 in a Phase 2 dose-expansion cohort. A summary of these patients as of the data cutoff is provided below.

The 17 patients in the Phase 1 portion of the study have been dosed IV across four Q2W dose levels (0.15 mg/kg and 0.5 mg/kg [1 patient, each], 1 mg/kg [3 patients], 3 mg/kg [6 patients]) and one Q4W dose level (3 mg/kg [6 patients]). The 23 patients in the Phase 2 portion have been dosed IV at 1 mg/kg Q2W. As of the data cutoff, 17 patients were still receiving study drug including 5 patients in Phase 1 (1 mg/kg IV Q2W [1 patient], 3 mg/kg IV Q2W [2 patients] and 3 mg/kg IV Q4W [2 patients]) and 12 patients in Phase 2.

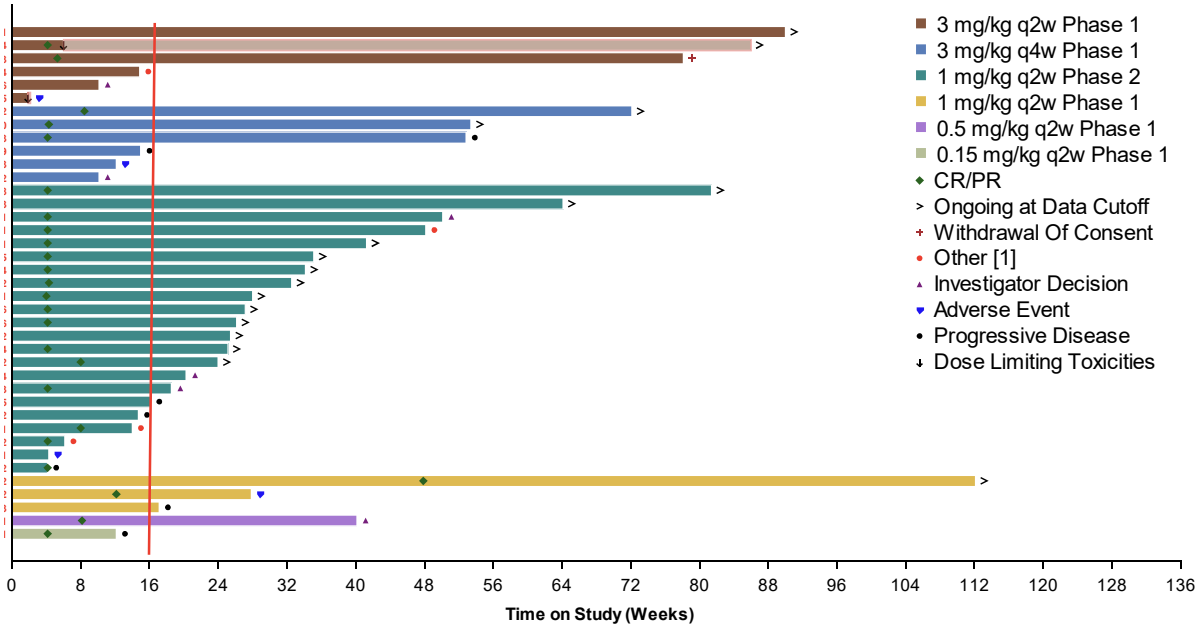
Ninety-eight percent of patients experienced at least 1 treatment emergent adverse event (TEAE) as of the data cutoff. One patient in 1 mg/kg IV Q2W (Phase 2) had not reported any TEAEs. Two patients reported 1 event each that was considered a dose limiting toxicities (DLT) both dosed with axatilimab 3 mg/kg IV Q2W (creatine phosphokinase [CPK] increase and an increase in amylase and lipase which required a 3-week delay in the patient's third dose). Eight patients reported a related TEAE which was ≥Grade 3 as follows: blood CPK increased (3 mg/kg Q2W, 2 patients and 3 mg/kg IV Q4W, 1 patient); aspartate aminotransferase (AST) increased (0.15 mg/kg and 3 mg/kg Q2W, 1 patient each); gamma-glutamyl transferase (GGT) increased (0.15 mg/kg and 3 mg/kg Q2W, 1 patient each); lipase increased (3 mg/kg IV Q2W and 3 mg/kg IV Q4W, 1 patient each); hypersensitivity (1 mg/kg IV Q2W, 1 patient); periorbital oedema (3 mg/kg IV Q4W, 1 patient); and septic arthritis staphylococcal (1 mg/kg IV Q2W, 1 patient). Four patients reported 7 serious related TEAEs as follows: abdominal distension, face oedema, hypersensitivity, neuropathy peripheral, oedema peripheral, and septic arthritis staphylococcal (1 mg/kg IV Q2W, 1 patient each); and pyrexia (3 mg/kg IV Q2W, 1 patient)

Biochemical elevations reflect a consequence of CSF-1R blockade on Kupffer cells leading to an inhibition in the clearance of these enzymes, consistent with the mechanism of action of axatilimab and when asymptomatic have not been associated with clinical manifestations of hepatitis, pancreatitis, or rhabdomyolysis. Periorbital edema was observed in 2 patients (≤Grade 2); no additional CSF-1Ri class-effect associated TEAEs were observed.

Preliminary PK data are available from 7 of the 11 patients enrolled in the study as of 30 March 2020. [redacted] A dose-dependent increase in exposure was observed in groups given 0.15 to 3 mg/kg of drug. The C_{max} followed this trend and was consistent with other studies evaluating axatilimab. [redacted]

As of 22 October 2021, all but 12 patients had received at least 16 weeks of study treatment including 23 patients who had completed at least 24 weeks of study treatment. Of the 12 patients who had not received 16 weeks of study treatment, 6 came off study due to progressive disease or investigator decision and 6 discontinued treatment due to an adverse event or other reason. Of the 23 patients who had completed at least 24 weeks of study treatment, 17 were ongoing at the data cutoff. Duration of treatment and patient responses are shown in Figure 1.

Figure 1 Swimmer Lane Plot by Phase and Cohort Showing Duration on Study Drug and Responses as of 22 October 2021



As of 22 October 2021, all overall responses were partial response (PR) according to the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD (NIH Consensus Criteria). PRs or complete responses (CRs) have been observed in the esophagus, eyes, skin, joints/fascia, and mouth.

2.3. Benefit and Risk Analysis

To date, available axatilimab nonclinical and clinical data support clinical investigation in patients with cGVHD. The axatilimab IB provides a summary of known and expected benefits and risks of axatilimab. [redacted]

Due to the axatilimab mechanism of action (pharmacological inhibition of CSF-1R), axatilimab may induce dose-dependent and reversible increases in circulating levels of CPK, AST, alanine aminotransferase (ALT), glutamate dehydrogenase (GLDH), amylase and lipase (see IB for details). Kupffer cells in the liver (which are involved in the clearance of these enzymes) are in the macrophage lineage and susceptible to axatilimab inhibition of CSF-1R. The expected increases in these enzyme levels are related to decreased clearance from the blood, rather than from drug-induced liver injury and are not associated with any histopathological change. Laboratory assessments (ie, clinical chemistries, including tests for liver function) will be performed as specified in protocol to monitor patient's safety. Similarly, prolonged anti–CSF-1R blockade eliminates osteoclasts and is associated with increased levels of bone turnover markers, with preclinical studies supporting an overall positive impact on bone density and trabecular bone volume (Sauter 2014; Ambrosi 2021). [redacted]

Given the mechanism of action and clinical experience with axatilimab thus far, there are no ongoing or planned toxicity studies in animal models, including juvenile animal models.

Responses have been observed across all axatilimab dose levels evaluated in a pretreated cGVHD population (Figure 1). Three dose levels have been selected for evaluation across a range of doses which to date have been tolerable and manageable. This study will seek to address the fact that the minimum efficacious dose has not yet been identified. The study design aims to provide patients with maximal benefit from axatilimab and reduced unnecessary risk, by monitoring all potential risks and incorporating early stopping rules for futility and safety.

Given the underlying scientific basis for testing CSF-1R targeted therapy in cGVHD, the lack of treatment options in this cGVHD population, a study design which includes interim evaluation of doses for safety and futility and preliminary PK, pharmacodynamics, safety and evidence of clinical activity seen in the ongoing study SNDX-6352-0503, the risk of axatilimab in the proposed patient population is justified.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the overall response rate (ORR) of axatilimab at 0.3 mg/kg IV Q2W, 1 mg/kg IV Q2W, and 3 mg/kg IV Q4W in patients with cGVHD after failure of least 2 prior lines of therapy.	• ORR in the first 6 cycles as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD.
Key Secondary – Efficacy	
• To evaluate key secondary measures of clinical benefit	• Proportion of patients with a clinically significant improvement in modified Lee Symptom Scale score (mLSS).
Secondary – Efficacy	
• To evaluate secondary measures of clinical benefit.	• ORR on study 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 for any reason. • Sustained response rate (SRR) • Organ-specific response rate based on 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD • Joints and fascia response rate based on refined NIH response algorithm for cGVHD (Inamoto 2020) • Percent reduction in average daily dose (or equivalent) of corticosteroids • Proportion of patients who discontinue corticosteroid use after study entry. • Percent reduction in average daily dose (or equivalent) of calcineurin inhibitors • Proportion of patients who discontinue calcineurin inhibitors use after study entry

Objectives	Endpoints
Secondary – Safety	
• To evaluate the safety and tolerability of axatilimab in patients with cGVHD	• Frequency and severity of AEs and serious adverse events (SAEs) • Change from baseline in values for vital signs, safety laboratory parameters, physical and neurological examination, ECG and Karnofsky/Lansky performance scale
[redacted]	
Secondary – PK/Pharmacodynamic	
• To assess the plasma population PK (pop PK) profile of axatilimab in patients with cGVHD	• Axatilimab PK parameters and patient factors that may explain variability in drug exposure
• To assess pharmacodynamic profile of axatilimab	• Change from baseline in colony stimulating factor 1 (CSF-1), interleukin 34 (IL-34) levels and its association with cGVHD response
• To determine or assess the changes in monocyte level with response	• Change from baseline in circulating monocyte number and phenotype (CD14/16)
• To determine or assess the baseline in monocyte level with response	• Baseline circulating monocyte number and phenotype (CD14/16)
Secondary – Immunogenicity	
[redacted]	

Objectives	Endpoints
[redacted]	
Exploratory – Efficacy	
• To explore possible additional evidence of clinical benefit. •	[redacted] • Proportion of patients with Failure Free Survival (FFS) at Cycle 7 Day 1 and 1 year. FFS is defined as the time from randomization to addition of another systemic immune suppressive therapy for cGVHD, relapse of underlying malignancy, or death whichever is earlier. • Overall survival (OS) [redacted]

4. STUDY DESIGN

4.1. Overall Study Design

AGAVE-201 is a Phase 2, open-label, randomized, multicenter study to evaluate the efficacy, safety and tolerability of axatilimab at 3 different dose levels, in patients with recurrent or refractory active cGVHD who have received at least 2 prior lines of systemic therapy due to progression of disease, intolerability or toxicity. Disease progression is defined 1) by the NIH 2014 consensus criteria, either in terms of organ specific algorithm or global assessment or, 2) as active, symptomatic cGVHD for whom the physician believes that a new line of systemic therapy is required.

The study will consist of 3 periods: Screening, Treatment, and Follow-up. Throughout the study, patients will be evaluated as specified in the Schedule of Activities (SoA) (Section 1.2).

After signing informed consent, potential candidates will undergo screening procedures to determine eligibility. At enrollment, eligible patients will be randomized to one of 3 dose cohorts (axatilimab 0.3 mg/kg IV every 2 weeks [Q2W], 1 mg/kg IV Q2W, or 3 mg/kg IV Q4W). Patients must begin treatment (Cycle 1 Day 1) within 3 days of randomization/enrollment and will receive axatilimab from Cycle 1 Day 1, in 4-week (28-day) treatment cycles, until disease progression (as defined by the NIH 2014 consensus criteria), lack of efficacy by 9 months (Section 6.7.2), withdrawal of consent, or unacceptable toxicity. Following treatment discontinuation, patients will receive an End of Treatment (EOT) visit 30 days after the last dose of study drug and 2 further safety and disease evaluation visits at 60 and 90 days post last dose of study drug.

Simon's optimal 2-stage design will be implemented within each dose cohort. In the first stage 27 patients will be randomized to each of the 3 dose cohorts. To limit the potential exposure of patients to an inefficacious dose and obviate the need for a pause in accrual, the initial futility analysis will be based on an early endpoint (ie, overall response in the first 3 cycles). Each dose will be evaluated for futility and unacceptable toxicity as follows:

- IA #1: Futility assessment based on responses in the first 3 cycleswill be conducted. This assessment will occur when the first 27 patients in each cohort have had the opportunity to complete 3 cycles of therapy. If ≤6 patients achieve a response after the first 3 cycles of axatilimab (up to and including cycle 4, day 1 assessment), the randomization to this dose level may be stopped for futility. Safety assessment will occur at this IA. For IA # 1, the boundary for unacceptable toxicity is ≥8 out of the first 27 patients having a toxic event defined as any serious or severe (≥Grade 3) TEAE that is attributed to study drug. Grade 2 events that are considered treatment-related and result in medical intervention or hospitalization will be counted as a toxic event.
- IA #2: IA #2 will consist of an overall evaluation of available clinical data. It will be conducted when the first 27 patients in each cohort have had the opportunity to complete 6 cycles of therapy. If ≤9 patients achieve a response to axatilimab, the randomization to this dose level will be stopped for futility. For IA#2, given the full enrollment of the study as of this amendment, the rate of toxicity events will be provided for all treated patients and will be reviewed as part of the overall benefit/risk

assessment. For the overall benefit/risk assessment, a comprehensive safety and efficacy analysis will be provided to the IDMC:

- Safety for all participants.
- Efficacy for all participants who have had the opportunity to receive 3 cycles of axatilimab.

Study randomization will not pause while data from the interim analyses are being evaluated.

An Independent Data Monitoring Committee will evaluate all data that are available at the time of the data cut for the interim analyses, and provide a recommendation on continued use of the available axatilimab dose levels.

A final efficacy analysis will be performed when all patients have had the opportunity to complete 6 cycles of treatment with axatilimab. A dose level will be considered successful if ≥29 patients have had a response to axatilimab (PR or CR), as defined by NIH 2014 cGVHD criteria. The final boundary for efficacy will be re-calculated if there is over enrollment in the second stage of the design. For example, if the total number of randomized patients in a dose level is 80, this dose level will be considered successful if ≥32 patients have had a response to axatilimab.

At the final analysis, if 19 or more patients out of the total 70 patients experience a toxic event (the boundary will be recalculated if there is over enrollment), this will indicate a 90% posterior probability of the toxicity rate exceeding 20% and the final determination of acceptability of a given dose will be based on the overall benefit/risk indicated by review of the totality of evidence.

Patients enrolled into a Q2W regimen may be eligible to change to a Q4W dosing during the study, as described in Section 6.3. Additional dosing modifications for already enrolled patients may be implemented following IDMC recommendation on closing enrollment to one or more dose level cohorts and are specified in Section 6.2.1.

The on-treatment response criteria will be assessed every 4 weeks and at the EOT visit or discontinuation of the study intervention using 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD: CR, PR, lack of response (unchanged, mixed or progression).

4.2. Dose Justification

The doses selected for this Phase 2 study of axatilimab in patients with cGVHD are 0.3 mg/kg IV Q2W, 1 mg/kg IV Q2W, and 3 mg/kg IV Q4W.

[redacted]

4.3. Rationale for Study Design

This randomized, Phase 2 study is designed to further evaluate axatilimab at 3 dose levels (0.3 mg/kg IV Q2W, 1 mg/kg IV Q2W and 3 mg/kg IV Q4W) in patients with cGVHD.

[redacted]

This study is designed to reflect standard Phase 2 studies evaluating investigational agents in patients with cGVHD, at each of the dose levels selected. It incorporates interim analyses to limit patients' exposure to doses that do not provide sufficient efficacy or acceptable toxicity. The primary endpoint, ORR by Day 169 or Cycle 7, Day 1 (whichever is later), has been selected based on its use in other cGVHD studies and its apparent correlation with overall survival (Jagasia 2018, Jagasia 2019).

Based on data from SNDX-6352-0503, evaluation of axatilimab at the 3 selected dose levels to identify a minimum efficacious axatilimab dose or maximum acceptable dose is warranted. Furthermore, the primary endpoint selected for the study will enable robust evaluation of the efficacy data from patients dosed at the selected dose level(s). This approach will enable thoughtful development of axatilimab in an orphan population of high unmet medical need.

4.4. End of Study Definition

There will be 3 dosing arms: 0.3 mg/kg IV Q2W, 1 mg/kg IV Q2W, and 3 mg/kg IV Q4W. Total study duration for each patient will be up to 28 months (excluding survival follow-up) as follows:

Screening period:	Up to 28 days (1 month) prior to the first dose of study intervention
Treatment period:	Until unequivocal disease progression or unacceptable toxicity up to a maximum period of 2 years. Patients who continue to derive benefit after 2 years of treatment, administration may continue following consultation with sponsor.
Safety Follow-up period:	Up to 90 days (3 months) after the last administration of study intervention
Overall survival follow-up period:	After completing safety follow-up, patients will be contacted every 3 months to assess overall survival for up to 5 years.
End of Study:	The final contact with the last patient for survival follow-up.

5. STUDY POPULATION

5.1. Inclusion Criteria

To be eligible for participation in this study, participants must meet all the following:

Age

1. Patient must be 2 years of age or older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Patients who are allogeneic HSCT recipients with active cGVHD requiring systemic immune suppression.

   Active cGVHD is defined as the presence of signs and symptoms of cGVHD per 2014 NIH Consensus Development Project on Criteria for Clinical trials in cGVHD (Jagasia 2015).

3. Patients with refractory or recurrent active cGVHD despite at least 2 lines of systemic therapy.

   - Refractory disease 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 investigation therapy for cGVHD.
     - Patients who have not achieved a response within 3 months on their prior therapy for cGVHD and for whom the treating physician believes a new systemic therapy is required.
   - Recurrent cGVHD is active, symptomatic disease (after an initial response to prior therapy) as defined, based on the NIH 2014 consensus criteria, by organ-specific or global assessment or for which the physician believes that a new line of systemic therapy is required.

4. Patients may have persistent, active acute and cGVHD manifestations (overlap syndrome), as defined by 2014 NIH Consensus Development Project on Criteria for Clinical trials in cGVHD.

Diagnostic Assessments

5. Karnofsky Performance Scale of ≥60 (if aged 16 years or older); Lansky Performance Score of ≥60 (if aged <16 years).
6. Adequate organ and bone marrow functions evaluated during the 14 days prior to randomization as follows:

   - Absolute neutrophil count $\geq 1.0 \times 10^9$/L (without growth factors within 1 week of study entry)
   - Platelet count $\geq 50 \times 10^9$/L (without growth factor or transfusion within 2 weeks of study entry)
   - ALT and AST ≤ 2.5 × upper limit of normal (ULN) and total bilirubin ≤1.5 × ULN.

- For patients with suspected or documented liver cGVHD, ALT and AST ≤5 × ULN and total bilirubin ≤1.5 × ULN.

7. Creatinine clearance (CrCl) ≥30 mL/min based on the Cockcroft-Gault formula in adult patients and Schwartz formula in pediatric patients.

Sex

8. Male and/or female participants.

   Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   - Adolescent and adult male patients capable of fathering a child who are non-sterilized and who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the study intervention treatment period and 90 days after the last dose of study intervention. However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
   - Female patients, post-menarche, must provide evidence of either post-menopausal status or negative urinary or serum pregnancy test. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
     - Menarche, regardless of age, is defined as having had the first occurrence of menstruation.
     - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
     - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
     - Female patients of childbearing potential who are not abstinent and intend to be sexually active with a nonsterilized male partner must use at least 1 highly effective method of contraception from 14 days prior to randomization throughout the total duration of the study intervention treatment period and 90 days after the last dose of study intervention. Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the

withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

9. Concomitant use a of systemic corticosteroid is allowed but not required. Topical and inhaled corticosteroid agents are allowed. If a patient is taking corticosteroids at study randomization, the following criteria must be met:
   - Be on a stable dose of corticosteroids for at least 2 weeks prior to Cycle 1 Day 1.
10. Concomitant use of CNI or mTOR inhibitors (sirolimus or everolimus) is allowed but not required. The CNI or mTOR inhibitors 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 patient is taking either a CNI or mTOR inhibitor at study randomization, the following criteria must be met:
   - Be on a stable dose of CNI or mTOR inhibitor for at least 2 weeks prior to randomization.
   - The dose of the CNI or mTOR inhibitor must be within the therapeutic range.

Informed Consent

11. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. A parent/guardian should provide consent for pediatric patients unable to provide consent themselves; in addition, where applicable pediatric patients should sign their own assent form.

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has acute GVHD 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 Investigator Brochure), or any other conditions that would make the patient, in the opinion of the Investigator, unsuitable for the study.
6. Patients with acquired immune deficiency syndrome (AIDS).
7. Hepatitis B (defined as hepatitis B virus [HBV] surface antigen positive and HBV core antibody positive, with positive HBV deoxyribonucleic acid [DNA], or HBV positive core antibody alone with positive HBV DNA. Hepatitis C (defined as positive hepatitis C [HCV] antibody with positive HCV ribonucleic acid [RNA]).

8. Diagnosed with another malignancy (other than malignancy for which transplant was performed) within 3 years of randomization, unless previously treated with curative intent and approved by Sponsor's Medical Monitor (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).
9. Female patient who is pregnant or breastfeeding

Prior/Concomitant Therapy

10. Previous exposure to CSF-1R–targeted therapies.
11. Taking agents for treatment of cGVHD other than corticosteroids or either a CNI or mTOR inhibitor is prohibited. See Inclusion Criteria 9 and 10 for guidelines regarding the appropriate use of corticosteroids, CNI, and mTOR inhibitor in combination with study treatment.
12. For approved or commonly used agents, other than corticosteroids, CNI and mTOR inhibitor, a washout of 2 weeks or 5 half-lives, whichever is shorter, is required at study enrollment.

Prior/Concurrent Clinical Study Experience

13. Receiving an investigational treatment within 28 days of randomization.

Concurrent Studies

14. Patients should not be participating in any other interventional study. Pediatric patients are encouraged to also participate in the ongoing developmental studies of the Pediatric cGVHD Symptom Scale (PCSS).

Additional Medical Conditions

15. Patients with a of history of latent or active tuberculosis (TB) before screening; signs or symptoms suggestive of active TB upon medical history and/or physical examination; recent close contact with a person with active TB; positive QuantiFeron TB test at screening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

6.1. Study Intervention(s) Administered

Table 3 Study Intervention

Intervention Name	Axatilimab (SNDX-6352)
Type	Biologic
Dose Formulation	Solution for infusion
Drug Product Strength	[redacted] mg/mL
Unit Dose Strength(s)	mg/kg
Original Dosage Level(s)	0.3 mg/kg IV Q2W, 1 mg/kg IV Q2W (Day 1 and 15 of each 4-week cycle) or 3 mg/kg IV Q4W (Day 1 of each 4-week cycle)
Route of Administration	IV infusion via an infusion pump over [redacted]; time windows of [redacted] are permitted (ie, infusion time is [redacted]). The exact duration of infusion should be recorded in both source documents and electronic case report forms (eCRFs).
IMP definition	A new drug or biological drug that is used in a clinical investigation (FDA).
Sourcing	Study intervention will be provided to the site centrally by the Sponsor or designated representative.
Packaging and Labeling	Axatilimab is supplied as a [redacted] sterile, preservative free solution in [redacted], colorless, [redacted] closed with a rubber stopper and sealed with an aluminum overseal and flip-off cap. The [redacted] are single use only and contain no preservatives. Label text for the axatilimab vial will at a minimum include the protocol number, the contents of the vial (eg, axatilimab [redacted] mg/mL), lot number, storage conditions, and Sponsor name and address. Labels comply with regulatory requirements for investigational products.
Former Name(s) or Alias(es)	UCB-6352, SNDX-6352

6.2. Intrapatient Dose Escalation

Intrapatient dose escalation is not permitted. Dose adjustment(s) related to change in dosing schedule (Section 6.3.) are not considered dose escalations as the dose intensity remains unchanged.

6.3. Changes to Dosing Schedule

Patients enrolled into Q2W regimens may have their dosing regimens changed to Q4W if they meet the criteria provided in Section 6.3.1, 6.3.2 or 6.3.3. Changes to dosing schedule are not considered dose escalations as the dose intensity remains unchanged.

If, following a change in schedule from Q2W to Q4W, a patient progresses, they may return to a Q2W schedule. At the time of change from a Q2W to Q4W schedule and vice versa, the dose intensity must remain the same (ie, the dose intensity immediately before the change must equate to the dose intensity immediately after the change).

6.3.1. Patients Enrolled into the 1 mg/kg IV Q2W Dose Schedule

Patients who have had their Cycle 7 assessment and have achieved a PR/CR that has been sustained for at least 20 weeks or have not progressed may change their dose schedule from Q2W to Q4W.

6.3.2. Patients Enrolled into the 0.3 mg/kg IV Q2W Dose Schedule

Patients who have had their Cycle 7 assessment and have achieved a PR/CR that has been sustained for at least 20 weeks or have not progressed may change their dose schedule from Q2W to Q4W.

6.3.3. Patients Who Have Escalated to the 1 mg/kg IV Q2W Dose Schedule from 0.3 mg/kg Q2W

If a patient has experienced a PR/CR or has not progressed following dose escalation to 1 mg/kg IV Q2W (Section 6.2) and their best response is maintained for 20 weeks, they may change their dose schedule from Q2W to Q4W. [redacted]

6.3.4. Patients Who Have Previously Dose Reduced for Reasons of Toxicity

Patients who have previously dose reduced for a reason of toxicity, have had their Cycle 7 assessment, and have achieved a PR/CR that has been sustained for at least 20 weeks or have not progressed may change their dose schedule from Q2W to Q4W. [redacted]

6.4. Randomization to Axatilimab Dose Level

All patients will be centrally assigned to axatilimab dose in a 1:1:1 randomization ratio using an Interactive Response Technology (IRT). Patient assignments will be stratified for severity of cGVHD (mild/moderate vs. severe) by the 4-point scale and prior use of at least one of the following therapies: ibrutinib, ruxolitinib and belumosudil (prior therapy vs. no prior therapy). Before the study is initiated, the log-in information and directions for the IRT will be provided to each site. This study will be an open-label study.

6.5. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only patients enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention 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 and authorized site staff.
3. SNDX-6352 drug product must be diluted to [redacted] supplied in an infusion bag. No other drugs should be added to the solution for infusion containing SNDX-6352.
4. The dose amount required to prepare the SNDX-6352 infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing. If the patient experiences either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study intervention must be recalculated. For weight change <10%, the decision to recalculate the SNDX-6352 dose can be in accordance with institutional practice. There is no dose cap or need for adjusted weight when calculating the dose for patients with a high BMI.

5. The solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, the solution can be stored at room temperature for a maximum of 4 hours.
6. Drug should be administered via an infusion pump.
7. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
8. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.6. Study Intervention Compliance

Administration of axatilimab will be supervised by the Investigator or sub-Investigator. Any delegation of this responsibility must follow the standard procedures. Records of treatment administration for each patient will be kept during the study. Clinical research associates will review study intervention administration records and verify compliance with the Pharmacy Manual during site visits and at the completion of the study. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

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

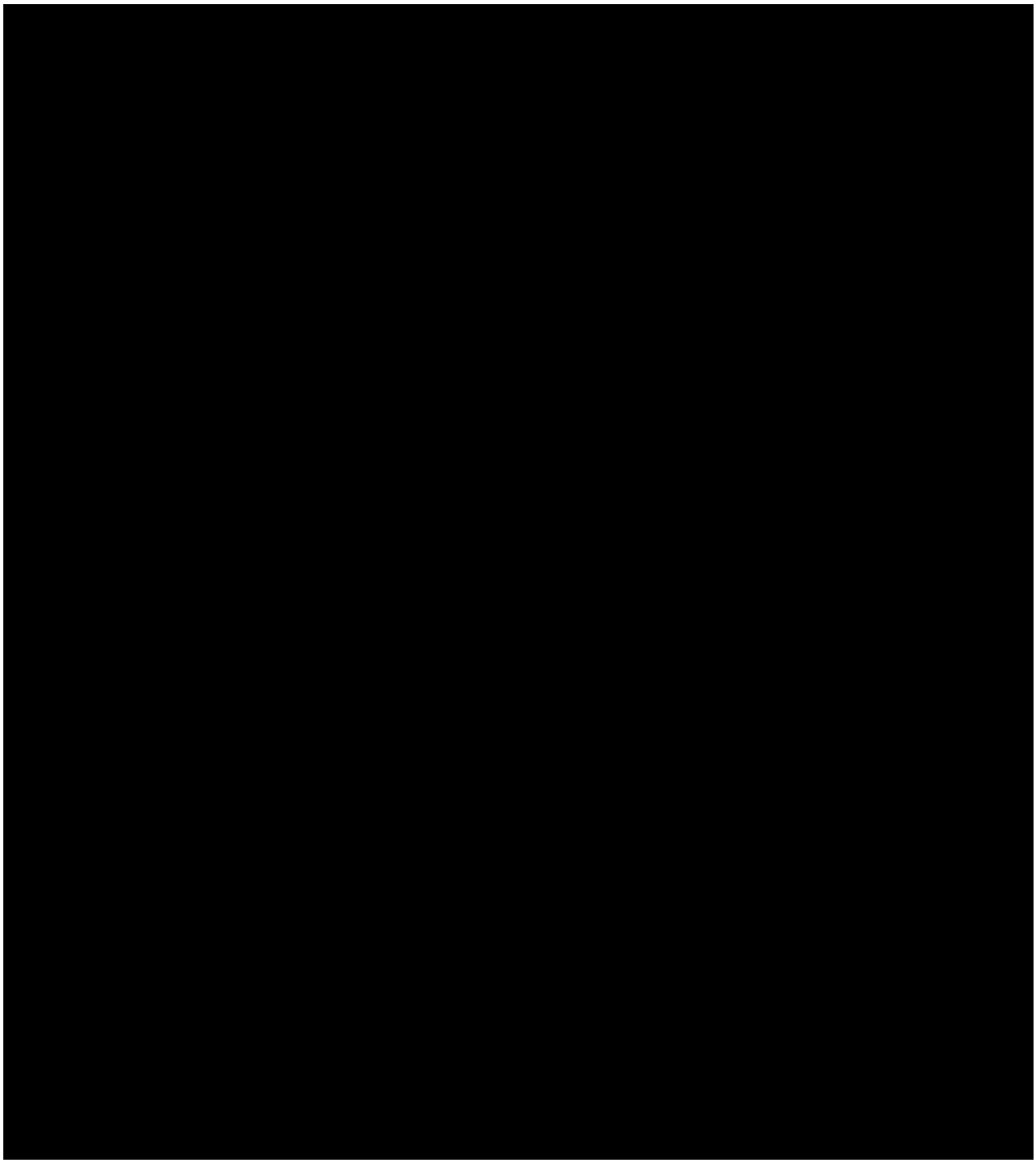
6.7. Stopping Rules and Dose Modifications

Dose delays and dose reductions (Table 4) will be allowed as described in Section 6.7.1. Patients who do not tolerate therapy after 2 dose level reductions from starting dose must withdraw from the study. Once the axatilimab dose has been reduced for reasons of toxicity, it cannot be re-escalated, however the dose schedule may be adjusted as provided in Section 6.3.4. Dose interruptions for reason(s) 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.

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, that is in the best interest of the patient. Such instances should be reported to the Sponsor’s Medical Monitor.

6.7.1. Guidelines for Toxicity Management

The guidelines for the management of toxicities are outlined as follows with each toxicity graded by the Investigator according to the NCI CTCAE, version 5.0.



[redacted]

6.7.1.2. Other Non-hematologic Toxicity

The rules for the management of other non-hematologic toxicities are outlined as follows in Table 6 with toxicities graded by the Investigator according to the NCI CTCAE, version 5.0.

Table 6 Other Non-hematologic Toxicity: Dose Modification Guidelines for Axatilimab

Toxicity	Dose modifications
Grade 4	Administer symptomatic remedies/start prophylaxis. Any Grade 4 events require permanent treatment discontinuation from axatilimab.
Grade 3	Administer symptomatic remedies/start prophylaxis. Hold axatilimab dose until recovery to Grade 2 under the following directions: 1. If axatilimab is held for ≤4 weeks, resume axatilimab at the next lower dose (Table 4). 2. If the axatilimab dose is held for more than 4 weeks, permanently discontinue axatilimab.
Grade 2	Administer symptomatic remedies/start prophylaxis. Do not hold axatilimab dose.

Note: Grade is per CTCAE 5.0

6.7.1.3. Hematologic Toxicity

The guidelines in Table 7 will be followed for determining the dose modifications based on hematologic status at the time of planned dosing.

Table 7 Hematologic Toxicity: Dose Modification Guidelines for Axatilimab

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

Note: Grade is per CTCAE 5.0

6.7.1.4. Axatilimab Infusion-Related Reaction

Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).

Patients experiencing an infusion-related reaction should be managed per institutional standard of care. Treatment recommendations for axatilimab infusion-related reactions are outlined in Table 8.

If a patient experiences an axatilimab infusion-related reaction, they may continue on study intervention treatment per guidance presented in Table 8. Patients who previously experienced an infusion-related reaction will receive a premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and acetaminophen/paracetamol (dosed per institutional guidelines) approximately 30 to 60 minutes prior to each subsequent dose of axatilimab. Prophylactic administration in the absence of prior infusion-related reaction is permitted as described in Section 6.9. Prophylactic corticosteroids are not permitted.

Table 8 Guidance for Treatment of Infusion-related Reactions

NCI-CTCAE Grade	Dose Modification	Toxicity Management
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen should be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen should be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions should be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** • 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. • Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** • Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute
Note: Grade is per CTCAE 5.0

If a Grade 2 infusion-related reaction does not improve or worsens after implementation of the modifications indicated in Table 8 (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 antihistamine and anti-pyretic is required. Prophylactic steroids are NOT permitted. If the patient has a second infusion-related reaction 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 patient removed from axatilimab treatment.

6.7.2. Discontinuation of Study Treatment for Lack of Efficacy

Study treatment should be discontinued if a patient does not achieve a PR within 9 months of initiating therapy. However, a patient may continue on study treatment if the PI/treating physician believes that the patient is deriving clinical benefit AND if the patient reports clinically meaningful symptomatic improvement (that may not be captured by the NIH criteria).

Any patient dosed at 0.3 mg/kg Q2W, 1 mg/kg Q2W or 3 mg/kg Q4W (or per dose adjustments) who experiences an unequivocal progression of cGVHD (initiation of new systemic therapy for cGVHD; increase in corticosteroid and/or CNI/mTOR inhibitor dose beyond those allowed by protocol) at any time should have their treatment discontinued.

6.8. Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating Investigator.

6.9. Concomitant Medication

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving within 28 days of randomization or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Vaccines, other than live vaccines, which are prohibited (Section 6.9.2), should be taken on a week when the axatilimab infusion is not administered.

Biologic therapies (intravenous immunoglobulins, monoclonal antibodies) used for non-antineoplastic and non-cGVHD causes are permitted. However, they should be administered on a week when the axatilimab infusion is not given.

Topical therapies (including topical corticosteroids) that the Investigator considers necessary for a patient'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/paracetamol 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. Use of corticosteroids for infusion reaction prophylaxis is not permitted.

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Corticosteroids, CNI and mTOR inhibitors

Adjustments to concomitant medications such as corticosteroids and/or CNI/mTOR inhibitors should be made as follows:

6.9.1.1. Corticosteroids

Patients may be taking a corticosteroid on study entry. The dose of corticosteroids may be tapered after the first 4 weeks of study intervention administration in patients who have achieved either a PR or CR, at the discretion of the Investigator. However, it is strongly recommended that

they are tapered at a rate of no more than 25% of the daily dose every 4 weeks and that they are tapered prior to discontinuation of any concomitant CNI or sirolimus.

For patients whose steroid dose has been tapered, one re-escalation of corticosteroids (up to starting dose) is allowed at the discretion of Investigator, up to 6 months from start of axatilimab.

In the case of exacerbation of cGVHD, patients may have one increase in corticosteroid dose of up to a maximum total daily dose of 0.9 mg/kg prednisone dose equivalent for a period of no longer than 8 weeks.

6.9.1.2. CNI or mTOR inhibitors

Patients may be taking a CNI or an mTOR inhibitor (sirolimus or everolimus) on study entry. The dose on Cycle 1 Day 1 must have been stable for at least 2 weeks (Inclusion Criterion 9). After the first post-baseline assessment a patient's CNI or mTOR inhibitor dose may be adjusted. Reasons for adjustment are as follows:

- To maintain a therapeutic dose - in this case the CNI or mTOR inhibitor dose may be increased above the dose at Cycle 1 Day 1.
- For a cGVHD flare – in this case the dose of CNI or mTOR inhibitor may be increased once above the dose at Cycle 1 Day 1.
- If patient is receiving a fixed dose of a CNI or an mTOR inhibitor and a new medication is started that significantly changes their metabolism. In such case, dose adjustment may be pursued following established evidence (eg, decrease in tacrolimus dose by 1/3 upon initiation of voriconazole). Reason for this change must be documented in the eCRF

A substitute CNI or mTOR inhibitor cannot be started unless change is indicated by toxicity or intolerance of previously used agent; reason for this change must be documented in the eCRF.

If after 4 weeks of study intervention the patient achieves a PR or CR, the dose of CNI or mTOR inhibitor may be reduced or discontinued; for such cases, doses may be increased subsequently 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, whenever possible it is recommended that the concomitant CNI or mTOR inhibitor be tapered after tapering of any concurrent corticosteroid.

6.9.2. Prohibited Medications

- Except for systemic corticosteroid, an mTOR inhibitor or a CNI, any other immune suppressive agents for treatment of chronic GVHD are not permitted.
  - This does not include agents for treatment of acute GVHD or the acute manifestations of overlap syndrome.
- Live virus vaccinations
- Antineoplastic systemic chemotherapy or biological therapy.
  - Concomitant use of medications indicated for maintenance therapy targeting the patient's previously treated underlying malignancy is allowed, including but not

limited to the use of proteasome inhibitors (e.g. ixazomib), endocrine therapies (e.g. tamoxifen, exemestane), and tyrosine kinase inhibitors (e.g. sorafenib, imatinib).

- Investigational agents other than axatilimab
- 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

7. DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

It may be necessary for a patient to permanently discontinue study intervention prior to planned completion of treatment regimen (see Section 6.7 for dose modification and toxicity management). If study intervention is permanently discontinued, the patient will remain in the study to be evaluated for up to 90 days post last dose of study intervention. See the Schedule of Activities (Section 1.2) for data to be collected at the time of discontinuation of study intervention (30 days post last dose of study intervention).

7.2. Patient Discontinuation/Withdrawal from the Study

Patients have the right to withdraw partially or fully from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Partial withdrawal of consent means that the patient does not wish to take study intervention any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in all subsequent study visits or procedures or follow-up contact). Full withdrawal of consent for a study means that the patient does not wish to receive further investigational treatment and does not wish to, or is unable to, continue further study participation. Any patient may fully or partially withdraw consent to participate in the study at any time during the study. The level of study withdrawal is to be noted in the source documentation.

In the event of discontinuation of all treatment or full withdrawal from the study, the Investigator will complete the End of Treatment form and indicate the date and the appropriate reason. To the greatest extent possible, the Investigator will attempt to complete all protocol-required tests and evaluations listed for the End of Treatment visit, Safety Follow-up visits, and Overall Survival Follow-up. If a patient fails to return for the necessary visits, every effort must be made to contact the patient and determine the reason(s); this should be recorded on the eCRF.

Reasons for permanently discontinuing study therapy and/or observation might include:

- Withdrawal of consent
- Progressive disease or exacerbation of any of the signs or symptoms of the disease assessed by Investigator.
- Administrative decision by the Investigator or Sponsor.
- Pregnancy
- Significant protocol deviation or patient noncompliance.
- Unacceptable toxicity
- A study treatment delay >4 weeks due to AEs.
- Need for intervention or therapy determined by the Investigator to be medically necessary that is precluded by protocol.

- The Investigator believes it is no longer in the patient's best interest to continue study therapy.

In addition, the Sponsor may decide to discontinue the trial prematurely for any reason.

7.3. Lost to Follow up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 in Section 10.1.

8. STUDY ASSESSMENTS

Planned timepoints for all study assessments are provided in the SoA (Table 1) and the PK and pharmacodynamic sample collection table (Table 2). Details required to carry out each assessment in addition to what is provided in the SoA, Sample Collection table and the footnotes is provided in the sections below.

8.1. Efficacy Assessments

It is preferred that all cGVHD assessments be done by the same health care provider who completed the C1D1 assessment. At minimum, the C7D1 assessment should be performed by the same health care provider who performed the C1D1 assessment. In addition, any assessments leading to changes in cGVHD therapy must be confirmed by the PI or primary treating physician.

8.1.1. Response Determination according to 2014 NIH Consensus definitions

Overall physician-assessed responses will be evaluated as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical trials in cGVHD (Lee 2015). CR 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 9 contains the Working Group proposed consensus definitions of CR, PR and progression for assessment of organ-specific responses as well as a global response determination.

Table 9 Response Determination for Chronic GVHD Clinical Studies based on Clinician Assessments

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 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 0 to 1
Eyes	NIH Eye Score 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 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 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 0 to 1
Upper GI	NIH Upper GI Score 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 0 to 1
Lower GI	NIH Lower GI Score 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

Organ	Complete Response	Partial Response	Progression
Liver	Normal ALT, alkaline phosphatase, and total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	Normal %FEV1 after previous involvement If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	Increase by 10% predicted absolute value of %FEV1 If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	Decrease by 10% predicted absolute value of %FEV1 If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 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 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

Source: Lee, 2015.

8.1.2. Response Determination for Pediatric Patients

No special assessments will be performed for pediatric patients. However, for younger patients, or those unable to comply, PFT assessments will include pulse oximetry and as clinically indicated, CT scan with inspiratory and expiratory phases to assess air trapping.

8.1.3. Physician-Reported Global and Organ Specific cGVHD Activity Assessment

Changes in cGVHD severity as defined by the NIH 2014 Consensus Criteria will be evaluated using physician reported global and organ-specific cGVHD activity assessment form (Section 10.5). The clinicians will provide a subjective assessment of current overall chronic GVHD severity on a 10-point category scale (no chronic GVHD, mild, moderate, severe) independent of the recorded NIH global severity score (Table 9, last line), 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 2015, Lee 2015).

8.1.4. Patient-Reported cGVHD Activity Assessment (mLSS)

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

The cGVHD mLSS questionnaire asks patients to indicate the degree of "bother" that they experienced during the past 7 days due to symptoms in 7 domains potentially affected by chronic GVHD (skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy,

emotional distress) (Lee 2002). Published evidence supports its validity, reliability, and sensitivity to cGVHD severity (Lee 2015, Merkel 2016, Teh 2020).

8.2. Safety Assessments

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the head, ears, eyes, nose and throat (HEENT), dermatological, respiratory, cardiovascular, gastrointestinal, neurological, and lymphatic, and musculoskeletal systems. Height will also be measured and recorded.
- Symptom-directed physical examination will be conducted as clinically indicated.
- Weight will be measured when complete or symptom-directed physical examinations are performed.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Neurological Examinations

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

8.2.3. Vital Signs

- Vital signs, systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiration rate (breaths per minute), and temperature ºF or C; collection method per site practice), will be measured as per standard practice. If initial blood pressure measurement is abnormal, repeat blood pressure measurement while the patient is in a semi-supine position after resting 5 minutes.
- The same units and mode should be used for a patient across all measurements.

8.2.4. Electrocardiograms

- Triplicate 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- Each time at which triplicate ECGs are clinically indicated, 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.
- ECGs will be recorded after the patient has rested in a supine position for at least 10 minutes.
- If a clinically significant abnormal ECG (Grade 3 or above by CTCAE v5.0) is reported, the ECG needs to be reviewed by a cardiologist.

8.2.5. Karnofsky/Lansky Performance Status

The Karnofsky/Lansky Performance Status allows patients to be classified as to their functional impairment on a scale from 0 to 100. 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 patients. The Karnofsky Scale is designed for patients aged 16 years and older, and the Lansky scale is designed for patients less than 16 years old (Lansky 1987). The Karnofsky scale is widely used validated tool in oncology settings, especially HSCT (Schag 1984, Crooks 1991, O'Toole and Golden 1991).

The Karnofsky and Lansky performance status are presented in Table 10.

Table 10 Karnofsky/Lansky Performance Status

Score	Karnofsky (for patients ≥16 years)	Lansky (for patients < 16 years)
	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, TV)
10	Moribund, fatal processes progressing rapidly	Completely disabled, not even passive play
0	Death	Death

8.2.6. Clinical Safety Laboratory Assessments

- See Appendix 10.1 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient'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 intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

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 AEs that are serious, considered related to the study intervention or study procedures, or that caused the patient to discontinue the study intervention and/or the study (Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Table 11 summarizes the different observation periods for AEs, SAEs, and adverse event of special interest (AESI).

Table 11 Adverse Event Observation Periods

Type of Event	Adverse Event	Serious Adverse Event	AESI with study drug
Reporting period	From consent until 90 days after the end of treatment	From consent until 90 days after the last dose of study treatment for all SAEs, and any time after the end of study for SAEs believed to be related to study intervention	From consent until 90 days after the last dose of study treatment, or 30 days after the initiation of a new anti-cancer therapy or any new therapy for GVHD, whichever is earlier
Reporting Timelines to the Sponsor	Entered into the clinical database on an ongoing basis	Within 24 hours	IRR Within 24 hours Infections: Entered into the clinical database on an ongoing basis

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

The Investigator is responsible for ensuring that all AEs observed by the Investigator or reported by patients are properly captured in the patient's medical records and reported in the eCRF.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

If a patient has an AE recorded as COVID-19, the date of the positive COVID test should also be recorded, if the patient subsequently has a negative COVID test, the date of this test should also be recorded.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Sections 10.3.2 and 10.3.3, respectively), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3.5).

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patient and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators, as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female patients, and female partners of male patients, will be collected after the start of study intervention and until 90 days after the last dose of study intervention.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- All female patients, and female partners of male patients becoming pregnant must be followed to completion/termination of the pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in patients with cGVHD and can be serious/life threatening:

- Disease progression: if disease progression occurs, record the date first documented in the EOT visit eCRF. Signs and symptoms related to PD should be reported in the appropriate cGVHD eCRF (if changed from baseline and meet progression criteria) or as an SAE if the event in question meets the criteria for seriousness.

Because these events are typically associated with the disease under study, they will not be reported to health authorities according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the corresponding cGVHD eCRF in the patient's CRF within the appropriate time frame.

8.4. Treatment of Overdose

Any overdose or incorrect administration of study intervention should be noted on the Study Drug Administration eCRF (including quantity of the excess dose and the duration of the overdose). AEs associated with an overdose or incorrect administration of study intervention should be recorded on the AE eCRF.

For this study, a study intervention overdose will be defined as a dose [redacted] mg/kg. No specific information is available on the treatment of overdose of SNDX-6352.

The overdose will not be considered an SAE unless the outcome of the overdose meets seriousness criteria. All reports of overdose with and without an adverse experience must be reported within 24 hours to one of the individuals listed on the Sponsor contact information page found in the Administrative Binder. The patient should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional standards of care.

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 patient.

8.5. Pharmacokinetics

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

Refer to the Study Laboratory Manual for instructions on sample collection and shipment to the central laboratories.

Other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to immune modulation, disease processes and pathways associated with disease state, and/or mechanism of action of axatilimab.

Samples may be stored for a maximum of 10 years (or according to local regulations) following the last patient's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to axatilimab.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypothesis

There are three randomized arms in the study with three different dose levels. The primary objective in each arm is to determine the efficacy of axatilimab with respect to ORR in the first 6 cycles. In each arm, the study will test the null hypothesis that the ORR in the first 6 cycles is ≤30% versus the alternative hypothesis that the ORR in the first 6 cycles is >30%.

9.2. Sample Size Determination

The sample size was calculated to provide adequate power for testing the statistical hypotheses regarding the primary endpoint of ORR in the first 6 cycles. Based on Simon's optimal 2-stage design, a total of 70 patients in each arm will provide approximately 90% power to detect a true ORR in the first 6 cycles of 50% with a 1-sided significance level of 0.025 in the arm.

The study will enroll patients in each arm in two stages, with 27 patients enrolled in the first stage. An IA in each arm will be conducted when the first 27 patients have had the opportunity to complete 3 cycles of therapy, and the dose will be evaluated for futility or unacceptable toxicity. In addition, a futility assessment may also be conducted at the time when each patient has had the opportunity to complete 6 cycles of therapy. Details of the IA are described in Section 9.4.5.

A final efficacy analysis will be performed when all patients have had the opportunity to complete 6 cycles of treatment with axatilimab. A dose level will be considered successful if ≥29 patients have had a response to axatilimab (PR or CR), as defined by NIH 2014 cGVHD criteria. The final boundary for efficacy will be re-calculated if there is over enrollment in the second stage of the design. For example, if the total number of randomized patients in a dose level is 80, this dose level will be considered successful if ≥32 patients have had a response to axatilimab.

At the final analysis, if ≥19 patients out of 70 patients experience a toxic event (the boundary will be recalculated if there is over enrollment), this will indicate a 90% posterior probability of the toxicity rate exceeding 20%, and the final determination of acceptability of a given dose will be based on the overall benefit/risk indicated by review of the totality of evidence.

9.3. Population for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-treat Analysis Set (ITT)	ITT Analysis Set for each dose level consists of all patients randomized to the dose level.
Response Evaluable Analysis Set	Response Evaluable Analysis Set for each dose level consists of all patients who were randomized to the dose level, received at least one dose of study drug and had at least one post-baseline assessment.
Safety Analysis Set	Safety Analysis Set consists of all enrolled patients who received at least one dose of study drug during the study.

PK Analysis Set	PK Analysis Set consists of all patients who receive at least one dose of axatilimab and have at least one valid plasma concentration of axatilimab determined.
Pharmacodynamic Analysis Set	Pharmacodynamic Analysis Set consists of patients who are exposed to axatilimab and have sufficient post-baseline samples collected to permit pharmacodynamic analyses.

9.4. Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications will also be reflected in a protocol amendment. The SAP will be finalized before database lock and will describe the analysis populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses.

In general, summary tabulations will be presented that display the number of observations, mean, standard deviation, median, 25th percentile (first quartile), 75th percentile (third quartile), minimum, and maximum for continuous variables, and the number and percent (of non-missing values) per category for categorical data. Time-to-event data will be analyzed using the Kaplan-Meier method and results will be summarized by 25th, 50th (median) and 75th percentiles with associated 2-sided 95% CIs, as well as the percentage of censored observations.

The statistical analyses will be performed using SAS® version 9.4 or later (SAS Institute Inc, Cary NC). Programming specifications will be prepared that describe the datasets and variables created for this study. The datasets will be prepared using the most recent version of CDISC's Study Data Tabulation Model (SDTM) and Analysis Dataset Model (ADaM). The source datasets from which a statistical analysis is performed (including interim reviews) will be archived with the Sponsor.

9.4.1. Efficacy Analysis

Efficacy analyses will be performed on the ITT analysis set.

Endpoint	**Statistical Analysis Methods**
Primary	The ***primary efficacy endpoint*** is overall response rate (ORR) in the first 6 cycles, defined as the proportion of patients with objective response (OR) during the first 6 cycles, where the first 6 cycles is defined as the time from randomization up to Day 169 or the beginning of Cycle 7, whichever is later; and OR is defined as CR or PR as defined by the NIH Consensus Development Project on Clinical trials in cGVHD. Exact 95% confidence intervals using binomial distribution will be provided.
Key Secondary	Proportion of patients with a clinically significant improvement in normalized score using the cGVHD mLSS will be calculated along with exact 95% CIs.

Endpoint	Statistical Analysis Methods
Secondary	• ORR on study is defined as proportion of patients with OR anytime on study as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD. Exact 95% confidence intervals using binomial distribution will be provided. • The DOR is defined as the time of initial response of PR or CR until documented progression of cGVHD, or start of new therapy, or death for any reason. DOR will be summarized descriptively using the Kaplan-Meier method. • SRR defined as proportion of patients with sustained response. The sustained response is defined as OR lasting for at least 20 weeks (140 days) from the time of initial response. Responses by organ system will be assessed based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD. • Organ-specific response rate defined as the proportion of patients with OR for the nine individual organs based on 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD (Skin, Eyes, Mouth, Esophagus, Upper GI, Lower GI, Liver, Lungs and Joints and Fascia) will be summarized with exact 95% CIs. • Joints and fascia response rate defined as the proportion of patients with Joints and Fascia response based on refined NIH response algorithm for cGVHD will be calculated along with 95% CIs. • Percent reductions in average daily doses (or equivalent) of corticosteroid after study entry will be summarized descriptively along with 95% CIs. • Proportion of patients who discontinue corticosteroid use after study entry will be summarized along with exact 95% CIs. • Percent reductions in average daily doses (or equivalent) of calcineurin inhibitors after study entry will be summarized descriptively along with 95% CIs. • Proportion of patients who discontinue calcineurin inhibitors after study entry will be summarized along with exact 95% CIs.

Endpoint	Statistical Analysis Methods
Exploratory	[redacted] • FFS is defined as the time from randomization to addition of another systemic immune suppressive therapy for cGVHD, relapse of underlying malignancy, or death whichever is earlier. The proportion of patients with FFS at Cycle 7 Day 1 (Day 168) and Cycle 14 Day 1 (1 year) will be calculated along with 95% CIs. • Overall survival is defined as time from randomization to the date of death (due to any cause). Patients who are alive or lost to follow-up (as of the data analysis cutoff date) will be censored. The duration of OS will be summarized descriptively using the Kaplan-Meier method along with 95% CIs. • Time to response will be calculated for patients who achieve a CR or PR. For such patients, TTR is defined as time from randomization to the first date the patient achieved a PR or CR. The duration of TTR will be summarized descriptively. [redacted]

9.4.2. Safety and Tolerability Analysis

All safety analyses will be performed on the Safety Analysis Set. Safety will be assessed by clinical review of all relevant parameters including vital sign measurements, Karnofsky/Lansky performance status, AEs, SAEs, physical and neurological examinations, ECG results, and laboratory values. Summary tables and listings will be provided for all reported TEAEs, defined as AEs that start on or after the first administration of study treatment. The reported AE term will be assigned a standardized preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse event will be summarized based on the numbers and percentages of patients experiencing the event by MedDRA system organ

class and preferred term. If a patient experiences repeat episodes of the same AE, then the event with the highest severity grade and strongest causal relationship to study treatment will be used for purposes of incidence tabulations.

Tabular summaries will be provided for the following:

- All TEAEs
- TEAEs by relationship to study drug treatment and maximum severity grade
- TEAEs with action of study intervention treatment delayed, dose skipped, or dose reduced
- TEAEs with action of study treatment discontinued
- SAEs
- Changes in Karnofsky/Lansky performance status score
- Changes in chemistry and hematology parameters
- Changes in vital signs, weight and ECGs

9.4.3. Pharmacokinetic Analyses

Plasma samples for population PK assessment will be analyzed for concentrations of axatilimab. A population PK modeling approach will be used to describe the PK of axatilimab in the target patient population. PK parameters such as clearance and volume of distribution will be defined for patients receiving axatilimab. In the analysis, a number of covariates, including patient demographic variables (eg, age, gender, body weight, and race) clinical laboratory parameters (eg, AST, ALT, CrCL) and concomitant medications will be evaluated to determine if they contribute to differences in PK estimates among individuals.

A separate PK analysis plan will be prepared prior to data analysis. Data from other studies of axatilimab may be pooled for this analysis, if necessary, for robust model identification.

9.4.5. Interim Analysis

Interim analyses will occur when the first 27 patients in each cohort have had the opportunity to complete 3 (IA #1) and 6 (IA #2) cycles of therapy. The addition of the first IA to the Simon's 2-stage design does not inflate Type I error. With the assumption that 70% of responses occur in the first 3 cycles, adding this futility assessment slightly reduces the overall study power from 90% to 83% but provides a 67% probability of early stopping under the null to reduce potential over-randomization to a futile dose.

Toxicity evaluation will coincide with the futility assessments. Toxic event is defined as any serious or severe (≥Grade 3) TEAE that is attributed to study drug. Grade 2 events that are considered treatment-related and result in medical intervention or hospitalization will be counted as a toxic event.

For IA #1, the stopping rules for unacceptable toxicity are established using Bayesian method using a maximum acceptable toxicity rate of 20%, a θ prior distribution (1,1), and a posterior probability of 90%. The operating characteristics of this design are calculated using Bayesian Toxicity Monitoring Software (BTM) by The University of Texas MD Anderson Cancer Center. Further details will be provided in the SAP.

Simon's optimal 2-stage design will be implemented within each dose cohort. In the first stage 27 patients will be randomized to each of the 3 dose cohorts. To limit the potential exposure of patients to an inefficacious dose and obviate the need for a pause in accrual, the initial futility analysis will be based on an early endpoint (ie, overall response in the first 3 cycles). Each dose will be evaluated for futility and unacceptable toxicity as follows:

- IA #1: Futility assessment based on responses in the first 3 cycleswill be conducted. This assessment will occur when the first 27 patients in each cohort have had the opportunity to complete 3 cycles of therapy. If ≤6 patients achieve a response after the first 3 cycles of axatilimab (up to and including cycle 4, day 1 assessment), the randomization to this dose level may be stopped for futility. Safety assessment will occur at this IA. For IA # 1, the boundary for unacceptable toxicity is ≥8 out of the first 27 patients having a toxic event defined as any serious or severe (≥Grade 3) TEAE that is attributed to study drug. Grade 2 events that are considered treatment-related and result in medical intervention or hospitalization will be counted as a toxic event.
- IA #2: IA #2 will consist of an overall evaluation of available clinical data. It will be conducted when the first 27 patients in each cohort have had the opportunity to complete 6 cycles of therapy. If ≤9 patients achieve a response to axatilimab, the randomization to this dose level will be stopped for futility. For IA#2, given the full enrollment of the study as of this amendment, the rate of toxicity events will be provided for all treated patients and will be reviewed as part of the overall benefit/risk assessment. For the overall benefit/risk assessment, a comprehensive safety and efficacy analysis will be provided to the IDMC:
  - Safety for all participants.
  - Efficacy for all participants who have had the opportunity to receive 3 cycles of axatilimab.

Study randomization will not pause while data from the interim analyses are being evaluated.

An Independent Data Monitoring Committee will evaluate all data that are available at the time of the data cut for the interim analyses, and provide a recommendation on continued use of the available axatilimab dose levels.

A final efficacy analysis will be performed when all patients have had the opportunity to complete 6 cycles of treatment with axatilimab. A dose level will be considered successful if ≥29 patients have had a response to axatilimab (PR or CR), as defined by NIH 2014 cGVHD criteria. The final boundary for efficacy will be re-calculated if there is over enrollment in the second stage of the design. For example, if the total number of randomized patients in a dose level is 80, this dose level will be considered successful if ≥32 patients have had a response to axatilimab.

At the final analysis, if 19 or more patients out of the total 70 patients experience a toxic event (the boundary will be recalculated if there is over enrollment), this will indicate a 90% posterior probability of the toxicity rate exceeding 20% and the final determination of acceptability of a given dose will be based on the overall benefit/risk indicated by review of the totality of evidence.

Table 12 Interim Analysis #1 Toxicity Stopping Boundaries (Rate = 0.20 with Prior [1,1] and Posterior Prob. of 0.90)

Total Number of Patients	Number of Patients with Toxicities Considered Unacceptable
27	≥8

10. APPENDICES

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - 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
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- A parent/guardian should provide consent for pediatric patients unable to provide consent themselves; in addition, where applicable pediatric patients should sign their own assent form.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within (28) days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of blood samples for optional future research. The Investigator or authorized designee will explain to each patient the objectives of the future research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for future research. Patients who decline to participate in this optional research will not provide this separate signature.

10.1.3. Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her 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.

10.1.4. Independent Data Monitoring Committee

An IDMC has been established for this study and specific guidelines on the operation and purpose of the IDMC is documented in a Charter. The committee includes at least three members, including a statistician and medical oncologists experienced in the treatment of cGVHD. Safety review meetings will be held as per the IDMC charter and as needed if any unexpected safety signals emerge during the course of the study. The IDMC will be responsible for independently evaluating safety data of patients enrolled to the study. Decisions on study

termination, amendment of the protocol, or cessation of patient recruitment will be made after recommendations from the IDMC have been assessed by the Sponsor.

10.1.5. Dissemination of Clinical Study Data

A clinical study report will be developed by the Sponsor at completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

10.1.6. Data Quality Assurance

- All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (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 and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator per ICH-GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- 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. Also, current medical records must be available.
- Source documents are original documents, data, and records from which the patient's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

10.1.8. Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. 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.

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.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study intervention development

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the local laboratory.
- In addition to the scheduled assessments (specified in SoA), clinical laboratory evaluations may be repeated during the treatment period per the Investigator's clinical judgment.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.
- Laboratory assessments will be done as specified in SoA (Section 1.3). Additional laboratory assessments may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 13 Protocol-Required Safety Laboratory Assessments

Hematology	
• White blood cell count (WBC) with differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)	• Hematocrit
• Hemoglobin	• Red blood cell (RBC)
• Platelet count	
Clinical Chemistries[a]	
• Alanine Aminotransferase (ALT)	• Aspartate Aminotransferase (AST)
• Alkaline phosphatase	• Gamma-glutamyl transferase (GGT)
• Total bilirubin (fractionated)	• Albumin
• Calcium	• Blood urea nitrogen (BUN)[b]
• Sodium	• Creatinine
• Chloride	• Potassium
• Glucose	• Bicarbonate
• Phosphorus/phosphates	• Lactic dehydrogenase
• Uric acid	• Total protein
• Amylase	• Magnesium (Screening only, unless clinically indicated)
• Lipase	• CPK

Urinalysis	
• Basic Urinalysis (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen; prior to each administration of study intervention treatment after C1 if clinically indicated)	• Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the Screening and EOT visits).
Other Laboratory Assessments	
[redacted]	
• Coagulation factors, including PT or International Normalized Ratio (INR) and aPTT (Screening only)	• Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential[c]
• HCV RNA[d]	

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 6.7 (stopping rules and dose modification).
[b] If urea level is reported by the local site laboratory instead of blood urea nitrogen (BUN), BUN level should be calculated formulas detailed in Section 10.2 and entered in the appropriate field in the eCRF.
[c] For female patients of child-bearing potential, a serum pregnancy test is required to be performed during screening and within 3 days before the first study intervention dose if the screening pregnancy test is performed more than 3 days before the first study intervention dose. A serum pregnancy is also required at the end of study. During the study, either urine or serum pregnancy tests are performed. Pregnancy testing is to be repeated every 4 weeks.
[d] Polymerase chain reaction is required and must be negative for HCV RNA in patients positive for HCV antibody.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment (ICH E6:1.2). • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, 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 progression of underlying disease). • Worsening of a pre-existing medical condition, (ie, diabetes, migraine headaches, gout) should be considered an AE if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening (ie, places the patient at immediate risk of death) The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. 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 of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Is an important medical event that although may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse drug experience when, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest for SNDX-6352 are by the Sponsor defined as:
• Infusion-related reactions including hypersensitivity reactions • Infections

10.3.4. Definition of Suspected and Unexpected Adverse Reaction

Suspected adverse reactions are defined as:
• any AE for which there is a reasonable possibility that the study intervention caused the AE. For the purposes of Sponsor regulatory safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study intervention and the AE.
Unexpected Adverse events are defined as:
• AE which is not listed in the reference safety information of the IB of the study intervention or is not listed at the specificity or severity that has been observed.

10.3.5. Recording, Assessment, and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF/SAE form. • It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Medical Monitor/Syndax in lieu of completion of the AE/SAE CRF/SAE form. • There may be instances when copies of medical records for certain cases are requested by the Medical Monitor/Syndax. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission. 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.
Assessment of Intensity
AE severity will be evaluated by the Investigator in accordance with the NCI CTCAE v5.0. For AEs that are not adequately addressed in the NCI CTCAE, the Investigator should classify the intensity of the AE using the following guidelines: • Grade 1: Mild: Aware of sign or symptom, but easily tolerated; no intervention needed • Grade 2: Moderate: Discomfort enough to cause interference with usual activity, minimal non-invasive intervention indicated (eg, short course of antibiotics) • Grade 3: Severe: Medically significant but not immediately life-threatening; incapacitation with inability to work or do usual activity • Grade 4: Life-threatening: Refers to an event in which the patient was at risk of death at the time of the event, as judged by the Investigator; urgent/emergent intervention indicated. This category should not be used for an event that hypothetically might have caused death if it were more severe. • Grade 5: Fatal outcome. It will be left to the Investigator's clinical judgment to determine whether an AE is of sufficient severity to require the patient's removal from treatment or from the study. A patient may also voluntarily withdraw consent from treatment due to what she/he perceives as an intolerable AE. If either of these situations arises, the patient should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator must make a judgment regarding whether or not the AE was related to the study drug. The Investigator will also review laboratory test results and determine whether an abnormal value in an individual patient represents a clinically significant change from baseline and whether or not the change is related to study intervention. Guidelines for assessing relationship to study intervention are as follows:

The study intervention relationship will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by study intervention?" The causal relationship between an AE and the study intervention will be determined by the following definitions:

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possibly Related – There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (eg, the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (eg, the participant's clinical condition, other concomitant treatments).

Not Related - The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

When assessing the relationship between administration of the study drugs and the AE, the following should be considered:

- Follows a temporal sequence from administration of investigational product
- Is a known response to the investigational product based on clinical or preclinical data
- Could not be explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other therapy administered to the patient
- Disappears or decreases upon cessation or reduction of dose of investigational product
- Reappears or worsens when investigational product is reinstated

The Investigator must continue to follow all AEs until resolution or the Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study. The Investigator must promptly report to his or her IRB/EC all unanticipated problems involving risks to patients, per institutional

requirements. This includes death from any cause and all SAEs reasonably or possibly associated with the use of study drug according to IRB/EC procedures.
Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Medical Monitor/Syndax 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. • [If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide Medical Monitor/Syndax with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6. Reporting of SAEs and AESI

SAE/AESI Reporting to Syndax via email or facsimile
• On discovery, all SAEs and infusion-related reactions, including hypersensitivity reactions AESIs should be immediately reported (latest within 24 hours of knowledge of the event) to Syndax by completing the SAE report. Infusion-related reactions, including hypersensitivity reactions AESIs, regardless of seriousness, are reported via an SAE report form. If the AESI does not meet the criteria for seriousness, the form should be completed, but no criteria for seriousness should be checked on the SAE form. The completed SAE form and supporting documents should be emailed to: **SyndaxSAEReporting@syndax.com** Please note that this email address is for the reporting of SAE, AESI, and pregnancy information only. Back-up reporting method: • Back-up reporting method to Syndax is fax of SAE form to 1-888-529-3580. • Contacts for SAE reporting can be found in Investigational Site File

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

Women will be considered postmenopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

Note: Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal 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 randomization.

Other conditions:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternative medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

Contraception Guidance:

Female patients of childbearing potential should be informed that taking study intervention may involve unknown risks to the fetus (unborn baby) if a pregnancy were to occur during the study. Specifically, the study intervention may have adverse effects on a fetus in utero.

See Inclusion Criterion 9 in Section 5.1 for study requirements for female and male patients.

Patients with childbearing potential should use highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 14. These contraceptive methods must be used from 14 days prior to randomization and for at least 90 days after the last dose of study intervention. Patients must adhere to the contraception requirement for the duration of the study and during the follow-up period to participate in the study. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 14 Highly Effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	• Implants: Etonogestrel-releasing implants: eg, Implanon® or Norplant® • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices: eg, NuvaRing® • Injection: Medroxyprogesterone injection: eg, Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: eg, Ortho Evra® • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] This is also considered a hormonal method

Collection of Pregnancy Information in female patients who become pregnant, and female partners of male patients

- Please refer to the Study Manual for details on the pregnancy reporting procedure and associated report form
- The Investigator will collect pregnancy information on any female patient or partner of a male patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study

10.5. Appendix 5: Rating Scales

10.5.1. Global cGVHD Activity Assessment – Clinician Report

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*

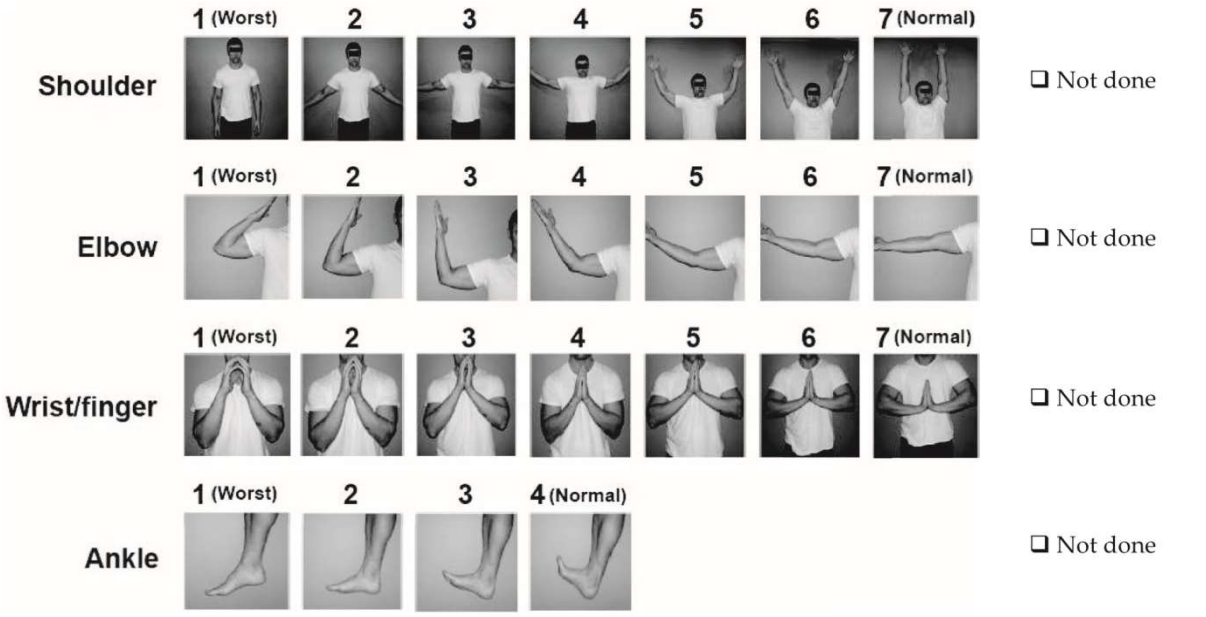
Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)		TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 min		Karnofsky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

Figure 1. Chronic GVHD Activity Assessment- Clinician Report.

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):_____				



❑ Not done

❑ Not done

❑ Not done

❑ Not done

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

Source: Lee, 2015.

10.5.2. cGVHD mLSS

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

Subscale Name	Items	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, 2002, Teh, 2020.

10.6. Appendix 6: Abbreviations

Abbreviation Term	Description
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALP	Elevation of Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
[redacted]	[redacted]
BUN	Blood Urea Nitrogen
cGVHD	Graft Vs. Host Disease
CPK	Creatine Phosphokinase
CNI	Calcineurin Inhibitor
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
[redacted]	[redacted]
CSF-1	Colony stimulating factor 1
CSF-1R	Colony stimulating factor 1 receptor
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECP	Extracorporeal photopheresis
ELISA	Enzyme-linked immunosorbent assay
EOT	End of treatment
FDA	Food and Drug Administration
FFS	Failure Free Survival
GGT	Gamma-Glutamyl Transferase
GLDH	Glutamate Dehydrogenase
GVL	Graft versus leukemia
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HEENT	Head, Ears, Eyes Nose and Throat

Abbreviation Term	Description
HSCT	Hematopoietic Stem Cell Transplantation
IA	Interim analysis
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IHC	Evaluated by Immunohistochemistry
IL	Interleukin
INR	International Normalized Ratio
ITT	Intent-to-Treat
IV	Intravenous
kg	Kilograms
mAb	IgG4 Monoclonal Antibody
mTOR	Mammalian target of rapamycin
NIH	National Institutes of Health
NK	Natural Killer
ORR	Overall Response Rate
PCSS	Pediatric cGVHD Symptom Scale
PFT	Pulmonary Function Test
PK	Plasma Pharmacokinetics
PR	Partial Response
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SoA	Schedule of Activities
TEAE	Treatment Emergent Adverse Event
TB	Tuberculosis
ULN	Upper Limit of Normal
WBC	White Blood Cell

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