CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2, Open-Label, Dose Escalation and Dose Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamic Activity, and Efficacy of SNDX-6352 in Subjects with Active Chronic Graft Versus Host Disease who have Received at least 2 Lines of Prior Therapy
Protocol Number:	SNDX-6352-0503
Compound Number:	SNDX-6352
Compound Name:	axatilimab
Study Phase:	Phase 1/2
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
Approval Date:	Version 10.0, 12 April 2022

SIGNATURE PAGE

Sponsor Signatory:

[redacted]

Electronically signed by: [redacted]
Reason: I am an approver.
Date: Apr 12, 2022 14:25 MDT

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Date

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INVESTIGATOR'S AGREEMENT

I have read the attached protocol (SNDX-6352-0503) entitled **"A Phase 1/2, Open-Label, Dose Escalation and Dose Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamic Activity, and Efficacy of SNDX- 6352 in Subjects with Active Chronic Graft Versus Host Disease who have Received at least 2 Lines of Prior Therapy"**, dated 12 June 2020, Version 8.0 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 V10, Amendment 10 (Site and FDA)	12 April 2022
Protocol V9, Amendment 9 (Site and FDA)	17 December 2020
Protocol V8, Amendment 8 (Site and FDA)	12 June 2020
Protocol V7, Amendment 7 (Site and FDA)	19 December 2019
Protocol V6, Amendment 6 (Site and FDA)	29 August 2019
Protocol V5, Amendment 5 (Site and FDA)	23 July 2019
Protocol V4, Amendment 4 (Site and FDA)	18 December 2018
Protocol V3, Amendment 3 (Site and FDA)	11 July 2018
Protocol V2.1, Amendment 2 (FDA only)	21 June 2018
Protocol V2, Amendment 1 (FDA only)	18 June 2018
Original Protocol V1 (Site and FDA)	15 May 2018

Amendment 10, 12 April 2022

Overall Rationale for the Amendment

Syndax has introduced the following modification to protocol V9.0; these changes are presented in order of importance:

Section # and Name	Description of Change	Brief Rationale
6.7 Dose Modification	Subsection 6.7.1, Axatilimab Taper, was added to define the option of axatilimab taper as an alternative to immediate drug discontinuation.	Taper of cGVHD therapies is a common medical practice that may mitigate risk of cGVHD flare during discontinuation. Measured discontinuation may limit occurrence of cGVHD flares. Data collected during this period may provide additional information on durability of axatilimab benefit.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1/2, Open-Label, Dose Escalation and Dose Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamic Activity, and Efficacy of SNDX-6352 in Subjects with Active Chronic Graft Versus Host Disease who have Received at least 2 Lines of Prior Therapy.

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, et al 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 macrophages by preventing differentiation and survival in tissue through the inhibition of colony stimulating factor 1 receptor (CSF-1R) has proven highly effective in animal systems.

SNDX-6352 is a humanized IgG4 monoclonal antibody (mAb) directed against CSF-1R with the potential to treat cGVHD through blockade of macrophage activity.

Objectives and Endpoints - Phase 1

Objectives	Endpoints
Primary	
• To characterize the optimal biologic dose (OBD) and identify recommended Phase 2 dose(s) (RP2D) of SNDX-6352 in subjects with cGVHD	• OBD and RP2D(s) of SNDX-6352
Secondary	
• To evaluate the safety and tolerability of SNDX-6352 in subjects with cGVHD	• Frequency and severity of adverse events (AEs) and serious adverse events (SAEs)
• To assess the plasma pharmacokinetics (PK) profile of SNDX-6352 in subjects with cGVHD	• Plasma PK of SNDX-6352
• To assess the pharmacodynamic (PD) profile of SNDX-6352	• Changes from baseline in colony stimulating factor 1 (CSF-1) and interleukin (IL)-34 levels and their association with cGVHD response

Objectives	Endpoints
	• Changes from baseline in circulating monocyte number (CD14/16)
• To evaluate changes in biomarkers following SNDX-6352 administration	• Changes from baseline in inflammation biomarkers that may include monocyte chemoattractant protein 1 (MCP1), Chemokine (C-C motif) ligand 3 (CCL3) and CCL5 expression
• To assess the immunogenicity of SNDX-6352	• Presence of anti-drug antibodies (ADA)

Objectives and Endpoints - Phase 2 Expansion Cohort(s)

For definition of efficacy endpoints, please refer to Table 12 in Section 9.4.3.

Objectives	Endpoints
Primary	
• To evaluate the efficacy of SNDX-6352 in subjects with cGVHD	• Proportion of subjects with complete response (CR) or partial response (PR) (Overall Response Rate [ORR]) at Cycle 7 Day 1 (Day 168)
Secondary	
• To evaluate the safety and tolerability of SNDX-6352 in subjects with cGVHD	• Frequency and severity of AEs and SAEs
• Secondary efficacy endpoints	• Best overall response rate (BOR) • Failure free survival (FFS) • Duration of response (DOR) • Sustained response rate (SRR) (CR or PR ≥ 20 weeks) • Organ-specific response rate based on 2014 National Institute of Health (NIH) Consensus Development Project on Criteria for Clinical Trials in cGVHD • Joints and fascia response based on refined NIH response algorithm for cGVHD (Inamoto, et al 2020)

Objectives	Endpoints
• To assess patient-reported outcomes (PROs) in subjects with cGVHD treated with SNDX-6352	• To assess changes in subject-reported symptom activity using the Lee cGVHD symptom scale. • Proportion of subjects with a ≥7-point improvement in normalized score
• To evaluate corticosteroid or calcineurin inhibitor use	• Percent reduction in average daily dose (or equivalent) or discontinuation of corticosteroid use after study entry • Percent reduction in average daily dose (or equivalent) or discontinuation of calcineurin inhibitor use, after study entry

Overall Design

This is a Phase 1/2, open-label dose escalation and dose expansion study to evaluate the safety, tolerability, PK/PD activity, OBD/RP2D(s) and efficacy of SNDX-6352 in subjects with active cGVHD who have failed at least 2 prior lines of therapy due to progression of disease, intolerability or toxicity. Subjects ≥18 years of age with active cGVHD who have erythematous rash involving >25% body surface area or a NIH mouth score of >4 must have received prior ibrutinib (IMBRUVICA®) therapy. The study will consist of a Screening period, a Treatment period, and a Safety Follow-up period.

In both study phases, study intervention will be given via intravenous (IV) infusion every 2 weeks (Q2W) until disease progression or unacceptable toxicity occurs for a maximum of 6 cycles. Subjects may receive study intervention in either an inpatient or outpatient setting. After 6 cycles of biweekly treatment, in subjects without cGVHD progression, the study intervention may be administered either biweekly or every 4 weeks (Q4W) at the Investigator's discretion in discussion with the Sponsor.

In both study phases, response criteria will be assessed every 28 days, and at the end of treatment 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). Window periods of ±1 day for Cycle 1 and ±3 days for each subsequent cycle will be allowed for response assessments.

Phase 1 Dose-Escalation Cohorts

Eligible subjects will be enrolled sequentially to evaluate escalating doses of SNDX-6352 as depicted below (for more information refer to Section 4.1 and Figure 1). For all cohorts, dose limiting toxicity (DLT) assessment window is 28 days from initiation of treatment with SNDX-6352 or administration of third dose (C2D1), whichever is later. For DLT criteria see Section 6.5. Decision to dose escalate will be made by the Safety Review Committee (SRC). Based on emerging data and the evaluation of the safety and tolerability data as a whole, it may

also be decided that accrual will take place at an intermediate dose level and/or alternative dosing schedule (e.g., 3 mg/kg Q4W or 4 mg/kg Q4W). The OBD is defined as the lowest safe dose with the highest rate of biologic activity. Biologic activity is determined by 100% reduction of non-classical monocytes at the time of dose interval and plateaued increase of circulating CSF-1 levels that persist for an entire dosing level.

Dose Escalation Scheme

Dose cohort	Dose levels of SNDX-6352	Dosing schedule****
1*	0.15 mg/kg (starting dose)	Q2W up to 12 cycles.***
2*	0.5 mg /kg	
3**	1 mg/kg	
4**	3 mg/kg	
4a**	2 mg/kg	

Q2W = every 2 weeks; Q4W = every 4 weeks
* Single subject cohort which can be expanded to 3+3 design depending on toxicity
** 3+3 design, 3 subjects per cohort which can be expanded to 6 subjects depending on dose limiting toxicity (DLT)
***If no progression, treatment may be continued after 6 cycles at Q2W or Q4W at investigator's discretion in discussion with Sponsor.
**** Based on emerging data, intermediate dose levels and/or alternative dosing schedules may be used

Phase 2 Dose-Expansion Cohort(s)

1 mg/kg Cohort

PK, PD, clinical response and safety data indicate that 1 mg/kg of SNDX-6352 is biologically active, induces organ specific responses and symptom improvement with no significant adverse events. This expansion cohort is designed to evaluate the preliminary efficacy of SNDX-6352 at 1 mg/kg. The dose-expansion phase will be conducted concurrently with the dose-escalation phase; however, subjects will be enrolled preferentially in the Phase 1 dose-escalation cohorts. Subjects may only be enrolled in this expansion cohort if enrollment in the current dose-escalation cohort is complete or assessment of DLTs and the recommendation for enrollment of the next dose escalation cohort by the SRC are pending. Intra-subject dose escalation to the 3 mg/kg dose is allowed after the dose has been cleared by the SRC in Phase 1 and after Investigator consultation with the Sponsor (for more information refer to Section 4.1 and Figure 2).

Disclosure Statement:

- The dose-escalation phase is a sequential group (dose-escalating) treatment study with up to 5 cohorts that is open-label.
- The dose-expansion phase is a parallel group treatment study with open-label cohorts.

Number of Subjects:

- In the dose-escalation phase, up to 30 subjects will be enrolled.
- In the dose-expansion phase, up to 22 subjects will be enrolled per cohort.

Intervention Groups and Duration:

The total study duration for each subject will be 16 months as follows:

Screening period:	Up to 28 days (1 month) prior to the first dose of study intervention
Treatment period:	Up to 365 days (12 months)
Safety Follow-up period:	Up to 90 days (3 months) after the last administration of study intervention

Safety Review Committee: Yes

1.2. Schedule of Activities (SoA)

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

[1] In case of early discontinuation, this visit (30 days after last dose of study intervention) will serve as end of study visit
[2] Includes age, race, and ethnicity
[3] 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 subject's disease or affect the treatment outcome.
[4] The Karnofsky Scale will be used for subjects aged 16 years and older, and the Lansky Scale will be used for subjects less than 16 years old
[5] If the Screening complete physical exam was performed within 7 days before C1D1, a symptom-directed physical exam may be performed at enrollment.
[6] Vital signs should also be obtained during or after the infusion, if clinically indicated
[7] Pre-dose

Study Procedure	Screening	Treatment Period							Safety Follow-Up		
		Cycle (each cycle consists of 28-days)							Days post last dose ±7 days		
		Cycle 1				Cycles 2 to 6		Cycles 7+			
Day in Cycle	**-28 to 0**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**+30[1]**	**+60**	**+90**
Visit Window	**NA**	**NA**	**±1D**	**±1D**	**±1D**	**±3D**	**±3D**	**±3D**	**±7D**	**±7D**	**±7D**
Safety Laboratory (hematology, & biochemistry)[8]	X	X	X	X	X[9]	As clinically indicated			X	X	
Coagulation factors	X					X[10]					
Bone markers (BAP, CTX)		X				X[11]					
HCV RNA[12]	X										
Urinalysis	X	X[13]	As clinically indicated								
Pregnancy testing[14]	X	X				X[15]		X	X		
SNDX-6352 administration		X		X		X	X	X			
DLT/toxicity assessment[16]						X[17]					
Adverse events		X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X

[8] Refer to Appendix 2 (Section 10.2) for full list of clinical laboratory tests
[9] For the 3 mg/kg Q4W cohort only, the Cycle 1 Day 22 safety laboratory sample is not required unless clinically indicated
[10] On Cycle 3 Day 1 only, before skin biopsy
[11] Bone turnover markers (bone alkaline phosphatase [BAP], C-terminal telopeptide [CTX]) will be collected pre-dose on C3D1
[12] Polymerase chain reaction is required and must be negative for HCV RNA in subjects positive for HCV antibody
[13] Performed only if Screening laboratory tests performed >7 days prior to C1D1
[14] For female subjects 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.
[15] Pregnancy testing is to be repeated every 2 cycles (8 weeks), on Day 1 of Cycles 3, 5,7, 9 and 11
[16] DLT/toxicity assessments will be done up to Cycle 2 Day 1, inclusive
[17] DLT assessment window is 28 days from initiation of treatment with SNDX-6352 or administration of third dose (C2D1), whichever is later

Study Procedure	Screening	Treatment Period							Safety Follow-Up		
		Cycle (each cycle consists of 28-days)							Days post last dose ±7 days		
		Cycle 1				Cycles 2 to 6		Cycles 7+			
Day in Cycle	**-28 to 0**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**+30[1]**	**+60**	**+90**
Visit Window	**NA**	**NA**	**±1D**	**±1D**	**±1D**	**±3D**	**±3D**	**±3D**	**±7D**	**±7D**	**±7D**
cGVHD response determination[18, 19, 20]		X				X		X			
Physician-reported global cGVHD activity assessment[21,18, 19]		X				X		X			
Lee cGVHD Symptom Scale		X				X		X			
Pharmacokinetics[22]		X	X	X	X[23]	X[24]		X			
Pharmacodynamics[25]		X	X	X	X[26]	X					
Anti-drug antibody[27]		X		X		X		X	X		
Tissue biopsy[28]	X					X[29]					

BAP = bone alkaline phosphatase; cGVHD = chronic graft versus host disease; CTX = C-terminal telopeptide; D = day; DLT = dose limiting toxicity; HCV RNA = hepatitis C virus ribonucleic acid; NA = not applicable

[18] Response evaluation will be according to 2014 NIH Consensus definitions; Window periods of ±3 days will be allowed for each response assessment

[19] 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.

[20] cGVHD assessments may be done every 12 weeks starting at Cycle 13

[21] Pulmonary Function Tests (PFTs) performed C1D1 prior to dosing, if PFTs have not been completed within 4 weeks of scheduled first dose. Frequency beyond C1 will be performed per standard of care

[22] PK sampling will occur at Cycle 1: predose, at 30 min (end of infusion), and at 1 hour (± 5 min), 8 hours (± 10 min) on Day 1 and Day 15; and at 168 hours (±24 hours) on Day 8. SNDX-6352 levels in plasma samples will be determined using a validated enzyme-linked immunosorbent assay (ELISA).

[23] For the 3 mg/kg Q4W cohort only, collect PK samples anytime on Cycle 1 Day 22

[24] PK samples will be collected predose on C2D1 and D1 of every cycle thereafter. Further PK sample collection will stop once axatilimab taper (Section 6.7.1.) commences.

[25] Plasma levels of a cytokine panel (may include CSF-1, IL-34, MCP-1, CCL3 and CCL5) and circulating monocyte number (CD14/16) will be collected on C1D1-predose, C1D8, C1D15-predose, C2D1-predose, C4D1-predose and end of treatment

[26] For the 3 mg/kg Q4W cohort only, collect a PD sample for circulating monocytes (CD14/16) anytime on Cycle 1 Day 22

[27] ADA will be captured at predose on C1D1, C1D15, C3D1, Day 1 of each following cycle, End of Treatment and 30-day follow up visit.

[28] Skin biopsy is only applicable for subjects with skin cGVHD

[29] Biopsy will be done on C3D1; skin biopsy only in subjects with skin cGVHD; lung biopsy only in subjects with transbronchial lung cGVHD

2. INTRODUCTION

2.1. Study Rationale

SNDX-6352 is a humanized IgG4 monoclonal antibody (mAb) with high affinity against colony stimulating factor-1 receptor (CSF-1R) under investigation for the treatment of advanced solid tumors and chronic graft vs. host disease (cGVHD). SNDX-6352 clinical development includes a completed Phase 1 study in healthy volunteers (SNDX-6352-0001) and an ongoing multiple ascending repeat dose study in patients with solid tumors (SNDX-6352-0502).

CSF-1R is expressed on cells of the mononuclear phagocyte lineage including immunosuppressive macrophages that accumulate within the tumor microenvironment. These tumor-associated macrophages (TAMs) are believed to play a key role in inhibiting anti-tumor T cell immune responses while promoting tumor progression. High levels of TAMs have been shown to correlate with poor prognosis for certain cancers and nonclinical studies have demonstrated that inhibition of TAMs can enhance anti-tumor immune responses. By binding to CSF-1R and blocking activation by its two known ligands, colony stimulating factor-1 (CSF-1) and interleukin-34 (IL-34), SNDX-6352 may affect the migration, proliferation, differentiation, and survival of TAMs. By targeting this key cellular player in the pathogenesis of cancer, CSF-1R blockade has the potential to slow disease progression and increase the clinical benefit of anti-tumor immunotherapeutic approaches [reviewed in (Cannarile, et al 2017; Quail and Joyce 2017)].

Nonclinical pharmacology studies with an anti-CSF-1R antibody have been completed in mouse models of IL-17 dependent skin and lung GVHD (Alexander, et al 2014). These studies established that donor bone marrow derived macrophages ($F4/80^{+}CSF\text{-}1R^{+}CD206^{+}iNOS^{-}$) were responsible for generating the fibrotic disease symptoms of cGVHD and that blockade of CSF-1 dependent monocyte recruitment, differentiation and proliferation ameliorated and prevented the development of cGVHD. Neither CCL2/CCR2 nor GM-CSF/GM-CSFR signaling pathways were required for macrophage infiltration or development of cGVHD. Importantly, in both 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, et al 2017)).

The standard of care for cGVHD has long consisted of steroid administration to relieve symptoms and delay disease progression, however this approach is associated with significant toxicity and emergence of resistance. Based on recent insight into the molecular mechanism involved in the disease related inflammatory process, interventions targeting kinases involved in these signaling pathways such as BTK, JAK1/2, and Syk have shown promising results in nonclinical and patient sample correlative studies (MacDonald, et al 2017) and of these, BTK inhibition has shown evidence of efficacy in Phase 2 clinical studies (Miklos, et al 2017). Therapies that directly target the donor derived, disease promoting macrophage have not yet been tested clinically. Targeting macrophages by preventing differentiation and survival in tissue

through the inhibition of CSF-1R has proven highly effective in animal systems (Alexander, et al 2014). Therefore, mAbs that are targeted to CSF-1R on the surface of macrophages, such as SNDX-6352, have potential as immunotherapeutic approaches to treat cGVHD.

Clinical data with CSF-1R targeted therapies in cancer patients have been reported for several agents including the small molecule PLX3397 and antibodies RG7155, JNJ-4036527, AMG820 and FPA008. These agents generally have been tolerated well with emerging class effects of periorbital edema, pruritus and elevated liver enzymes that may be related to on-target effects of CSF-1/CSF-1R blockade in Kupffer cells, a type of macrophage found in the liver, which are important for clearance of liver enzymes. Currently there are no safety data available for other CSF-1R targeted therapies in cGVHD as these agents have not yet been tested in this indication. See the IB for further details.

In vitro studies have demonstrated that SNDX-6352 binds to human CSF-1R (KD 4-8pM, Fc-tagged construct) and cross-reacts with cynomolgus monkey CSF-1R but not rodent CSF-1R. SNDX-6352 has been shown to inhibit potently both CSF-1 and IL-34 induced MCP-1 release from human monocytes (IC50, 270pM and 100pM respectively) and completely inhibits the viability of macrophages during the CSF-1-mediated differentiation process in vitro (IC50 455pM). A ligand (both CSF-1 and IL-34) blocking surrogate rodent antibody, Ab535, has been generated for preclinical studies in mice and inhibits tumor growth in models of colon (MC38), breast (MCF-7, MDA-MB-231) and prostate (PC-3) cancer and enhances activity of immune checkpoint blockade in the syngeneic MC38 tumor model.

Based on nonclinical data demonstrating that targeting CSF-1/CSF-1R prevents and treats cGVHD through depletion of donor derived macrophages, the Phase 1 study will evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics activity of SNDX-6352 in subjects with active cGVHD who have failed two prior therapies due to progression of disease, intolerability or toxicity. Up to 30 subjects are anticipated to participate.

SNDX-6352 PK and PD data from healthy subjects and solid tumor subjects indicate that all doses tested at Q2W, ranging from 0.15 mg/kg to 6 mg/kg have demonstrated evidence of biologic activity. Measurement of circulating non-classical monocytes levels, CSF-1 and IL-34 levels and receptor occupancy indicate a dose dependent effect of SNDX-6352 on these markers that correlate well with drug concentrations. Increased dosing effects the magnitude of change as well as duration of effect. At 1 mg/kg in both healthy subjects and solid tumor patients, depletion of non-classical monocytes is prolonged through approximately Day 10 of a 14-day dosing interval with recovery to baseline by the next dose. Doses higher than 1 mg/kg deplete monocytes for the full 14-day interval.

Preliminary data from the Phase 1 portion of this study indicate that both the PK and monocyte depletion effects at 1mg/kg are consistent with the data from the prior studies demonstrating that dose dependent biologic activity is conserved across healthy subjects, solid tumor and cGVHD subjects. These data justify 1 mg/kg as a potentially optimal biologic dose with early evidence of clinical benefit in cGVHD subjects treated at this dose level. The Phase 2 expansion phase will further evaluate preliminary efficacy of SNDX-6352 at 1 mg/kg in subjects with active cGVHD

who have failed two prior therapies due to progression of disease, intolerability or toxicity. Up to 22 subjects are anticipated to participate.

2.2. Background

cGVHD is an immune-mediated serious and life-threatening complication after allogeneic hematopoietic cell transplantation (HSCT), occurring in 30% to 70% of patients (Jagasia, et al 2015; Merkel, et al 2016). Most cases are diagnosed within the first year at a median of 4 to 6 months after HSCT, but 5-10% of cases are initially diagnosed beyond the first post-transplant year. cGVHD most often involves the skin and mouth, but almost any other organ system can be involved (Merkel, et al 2016); it may be restricted to a single organ or site or may be widespread, with profound impact on quality of life. The pathophysiology of the cGVHD may involve inflammation, cell-mediated immunity, humoral immunity, and fibrosis (Jagasia, et al 2015).

Treatment of cGVHD is currently based on steroids administration; systemic treatment begins with prednisone at 0.5 to 1 mg/kg per day, followed by a taper to reach an alternate-day regimen (Flowers and Martin 2015; MacDonald, et al 2017). Corticosteroids are typically administered for a median of 2 to 3 years, leading to substantial morbidity. 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, et al 2017). Approximately 50% to 60% of patients with cGVHD require secondary treatment within 2 years after initial systemic treatment; however, no consensus has been reached regarding the optimal choice of secondary agents (such as rituximab or imatinib) (Flowers and Martin 2015). Recently, the U.S. Food and Drug Administration (FDA) expanded the approval of Imbruvica® (ibrutinib, a kinase inhibitor) for the treatment of adult patients with (cGVHD) after failure of one or more treatments (Miklos, et al 2017).

As described in the study rationale above (Section 2.1), SNDX-6352, a humanized IgG4 mAb that blocks CSF-1R on the surface of macrophages, has potential as an immunotherapeutic approach to treat cGVHD.

A detailed description of the chemistry, pharmacology, efficacy, and safety of SNDX-6352 is provided in its Investigator's Brochure.

2.3. Benefit/Risk Assessment

The available nonclinical data and safety clinical data with SNDX-6352 to date support clinical investigation in subjects with cGVHD. Please refer to the SNDX-6352 IB for the available clinical and safety information of SNDX-6352.

Expected adverse events (AEs) that may be predicted to occur based on the pharmacological and toxicology properties of SNDX-6352, even if not yet observed with SNDX-6352 include periorbital edema, facial swelling, infusion reactions and pruritus.

Due to SNDX-6352 mechanism of action (pharmacological inhibition of CSF-1R), SNDX-6352 may induce dose-dependent and reversible increases in circulating levels of creatine kinase (CK),

aspartate aminotransferase (AST), alanine aminotransferase (ALT), and 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 SNDX-6352 inhibition of CSR-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 (i.e., clinical chemistries, including tests for liver function) will be performed as specified in protocol to monitor subject's safety.

A priori mechanistic considerations highlight a number of potential risks, which will be monitored in a clinical study setting. On the basis of the information currently available, the risk-benefit of SNDX-6352 is considered acceptable for cGVHD.

Given the underlying scientific basis for testing CSF-1R targeted therapy in cGVHD, the lack of treatment options in this cGVHD population, the conservative initial dose escalation and preliminary PK, PD, safety and preliminary evidence of clinical activity seen in the Phase 1 portion of this study , the risk of SNDX-6352 in the proposed patient population is justified.

Refer to the SNDX-6352 IB for additional information about the known and expected benefits and risks and reasonably expected adverse events of SNDX-6352.

3. OBJECTIVES AND ENDPOINTS

For definition of efficacy endpoints for Phase 1 (exploratory) and Phase 2 (primary and secondary), please refer to Table 12 in Section 9.4.3.

3.1. Phase 1 Dose Escalation

Objectives	Endpoints
Primary	
• To characterize the OBD and identify RP2D(s) of SNDX-6352 in subjects with cGVHD	• OBD and RP2D(s) of SNDX-6352
Secondary	
• To evaluate the safety and tolerability of SNDX-6352 in subjects with cGVHD	• Frequency and severity of AEs and SAEs
• To assess the plasma PK profile of SNDX-6352 in subjects with cGVHD	• Plasma PK of SNDX-6352
• To assess the PD profile of SNDX-6352	• Changes from baseline in CSF-1 and IL-34 levels and their association with cGVHD response • Changes from baseline in circulating monocyte number (CD14/16)
• To evaluate changes in biomarkers following SNDX-6352 administration	• Changes from baseline in inflammation biomarkers that may include MCP1, CCL3 and CCL5 expression
• To assess the immunogenicity of SNDX-6352	• Presence of ADA
Exploratory and Pharmacodynamic	
[redacted]	

Objectives	Endpoints
[redacted]	[redacted]

3.2. Phase 2 Dose Expansion

Objectives	Endpoints
Primary	
• To evaluate the efficacy of SNDX-6352 in subjects with cGVHD	• Proportion of subjects with CR or PR (ORR) at Cycle 7 Day 1 (Day 168)
Secondary	
• To evaluate the safety and tolerability of SNDX-6352 in subjects with cGVHD	• Frequency and severity of AEs and SAEs
• Secondary efficacy endpoints	• BOR • FFS • DOR • SRR (CR or PR ≥ 20 weeks) • Organ-specific response based on 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD • Joints and fascia response based on refined NIH response algorithm for cGVHD (Inamoto, et al 2020)
• To assess PROs in subjects with cGVHD treated with SNDX-6352	• To assess changes in subject-reported symptom activity using the Lee cGVHD symptom scale • Proportion of subjects with a ≥7-point improvement in normalized score
• To evaluate corticosteroid or calcineurin inhibitor use	• 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 inhibitor • Proportion of patients who discontinue calcineurin inhibitor use, after study entry

Objectives	Endpoints
Exploratory and Pharmacodynamic	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2, open-label, dose escalation and dose expansion study to evaluate the safety, tolerability, PK/PD, RP2D(s)/OBD and efficacy of SNDX-6352 in subjects with active cGVHD who have failed at least 2 prior lines of therapy due to progression of disease, intolerability or toxicity. Subjects ≥18 years of age with active cGVHD who have erythematous rash involving >25% body surface area or a NIH mouth score of >4 must have received prior ibrutinib therapy. The study will consist of a Screening period, a Treatment period, and a Safety Follow-up period.

In both study phases, study intervention will be given via IV infusion Q2W until disease progression or unacceptable toxicity occurs for a maximum of 6 cycles. Subjects may receive study intervention in either an inpatient or outpatient setting. After 6 cycles of biweekly treatment, in subjects without cGVHD progression, the study intervention may be administered either Q2W or Q4W, at the Investigator's discretion in discussion with the Sponsor.

In both study phases, response criteria will be assessed every 4 weeks and at the end of treatment 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). Window periods of ±1 day for Cycle 1 and ±3 days for each subsequent cycle will be allowed for response assessments.

At each study visit subjects will undergo assessments as specified in the Schedule of Activities (Section 1.2).

Dose Escalation

Eligible subjects will be enrolled sequentially to evaluate escalating doses SNDX-6352 as depicted in Table 1 and Figure 1. For all cohorts, DLT assessment window is 28 days from initiation of treatment with SNDX-6352 or administration of third dose (C2D1), whichever is later. For DLT criteria see Section 6.5. Decision to dose escalate will be made by the SRC. Based on emerging data and the evaluation of the safety and tolerability data as a whole, it may also be decided that accrual will take place at an intermediate dose level and/or alternative dosing schedule (e.g., 3 mg/kg Q4W or 4 mg/kg Q4W). The OBD is defined as the lowest safe dose with the highest rate of biologic activity. Biologic activity is determined by 100% reduction of non-classical monocytes at the time of dose interval and plateaued increase of circulating CSF-1 levels that persist for an entire dosing level.

Table 1: Phase 1 Dose Escalation Scheme

Dose cohort	Dose levels of SNDX-6352	Dosing schedule****
1*	0.15 mg/kg (starting dose)	Q2W up to 12 cycles.***
2*	0.5 mg /kg	
3**	1 mg/kg	
4**	3 mg/kg	
4a**	2 mg/kg	

* Single subject cohort which can be expanded to 3+3 design depending on toxicity
** 3+3 design, 3 subjects per cohort which can be expanded to 6 subjects depending on DLT
*** If no progression, treatment may be continued after 6 cycles at Q2W or Q4W at investigator's discretion in discussion with Sponsor.
**** Based on emerging data, intermediate dose levels and/or alternative dosing schedules may be used

The 2 lowest dose cohorts, 0.15 mg/kg and 0.5 mg/kg, will initially be a single-subject cohort. If the first subject enrolled into the 0.15 mg/kg cohort does not experience ≥ Grade 2 toxicity (non-DLT) during toxicity assessment window, the next enrolled subject will receive 0.5 mg/kg and if that subject treated at 0.5 mg/kg does not experience ≥ Grade 2 toxicity (non-DLT) during toxicity assessment window, enrollment to Cohort 3 (1 mg/kg) will be initiated utilizing 3+3 design. However, if the first subject in Cohort 1 (0.15 mg/kg) experiences ≥ Grade 2 toxicity (non-DLT) during toxicity assessment window, a 3+3 design will be utilized beginning with that dose and 2 additional subjects will be enrolled into Cohort 1 (total of 3 subjects); if any of these 3 subjects experience DLT, then 3 additional subjects will be enrolled (total of 6 subjects). If none of these 3 subjects experience DLT, enrollment will proceed to Cohort 2 and the same escalation rules will apply prior to proceeding to Cohort 3.

For Cohort 3 (1 mg/kg), initially 3 subjects will be enrolled. If no DLT observed from these 3 subjects, enrollment will proceed to Cohort 4 (3 mg/kg). However, if 1 of these 3 subjects at 1 mg/kg experiences a DLT during toxicity assessment window, 3 additional subjects will be enrolled into Cohort 3 (total of 6). If 1 out of 6 subjects in Cohort 3 experiences a DLT, enrollment will proceed to Cohort 4a (2 mg/kg), instead of Cohort 4 (3 mg/kg). If 2 out of 6 subjects at 1 mg/kg experience a DLT, dose will be de-escalated to a lower dose.

For Cohort 4a (2 mg/kg), if enrollment continues directly from Cohort 3 (1 mg/kg), then 3 subjects will initially be enrolled, if no DLT observed from these 3 subjects at 2 mg/kg, enrollment will proceed to Cohort 4 (3 mg/kg). However, if 1 of these 3 subjects experiences a DLT, 3 additional subjects will be enrolled into Cohort 4a at 2 mg/kg (total of 6). If 1 out of 6 subjects experiences a DLT, dose escalation will proceed to Cohort 4 (3 mg/kg). If 2 out of 6 subjects experience a DLT, dose will be de-escalated to a lower dose

For Cohort 4 (3 mg/kg), 3 subjects will initially be enrolled. If no DLT observed from these 3 subjects, then 3 additional subjects will be enrolled into Cohort 4 (total of 6). If 0 or 1 of these 6 subjects at 3 mg/kg experiences a DLT, this dose will be considered the maximum tolerated dose

(MTD) and aRP2D. If 2 out of 6 subjects at 3 mg/kg experience a DLT, dose will be de-escalated to Cohort 4a if less than 6 subjects are enrolled in Cohort 4a and enroll up to a total of 6 subjects. If 0 or 1 of these 6 subjects at 2 mg/kg experiences a DLT, this dose will be considered the MTD and a RP2D. Under both scenarios, if 2 out of 6 subjects experience a DLT, dose will be de-escalated to a lower dose.

The MTD is defined as the highest dose level at which no more than 1 of 6 subjects experienced a DLT. However, the OBD/RP2D may be a dose that is lower than MTD.

For subjects who are enrolled into dose cohort of 0.15 mg/kg, and 0.5 mg/kg, if they have tolerated the originally assigned dose without ≥Grade 2 study intervention related AE for 2 cycles, at Investigator's discretion, their dose may be subsequently escalated to higher dose that has been evaluated by SRC to have an acceptable safety profile. However, they will be included in the DLT evaluation only for the dose cohort to which they were originally assigned.

Figure 1: Phase 1 Dose Escalation Decision Tree

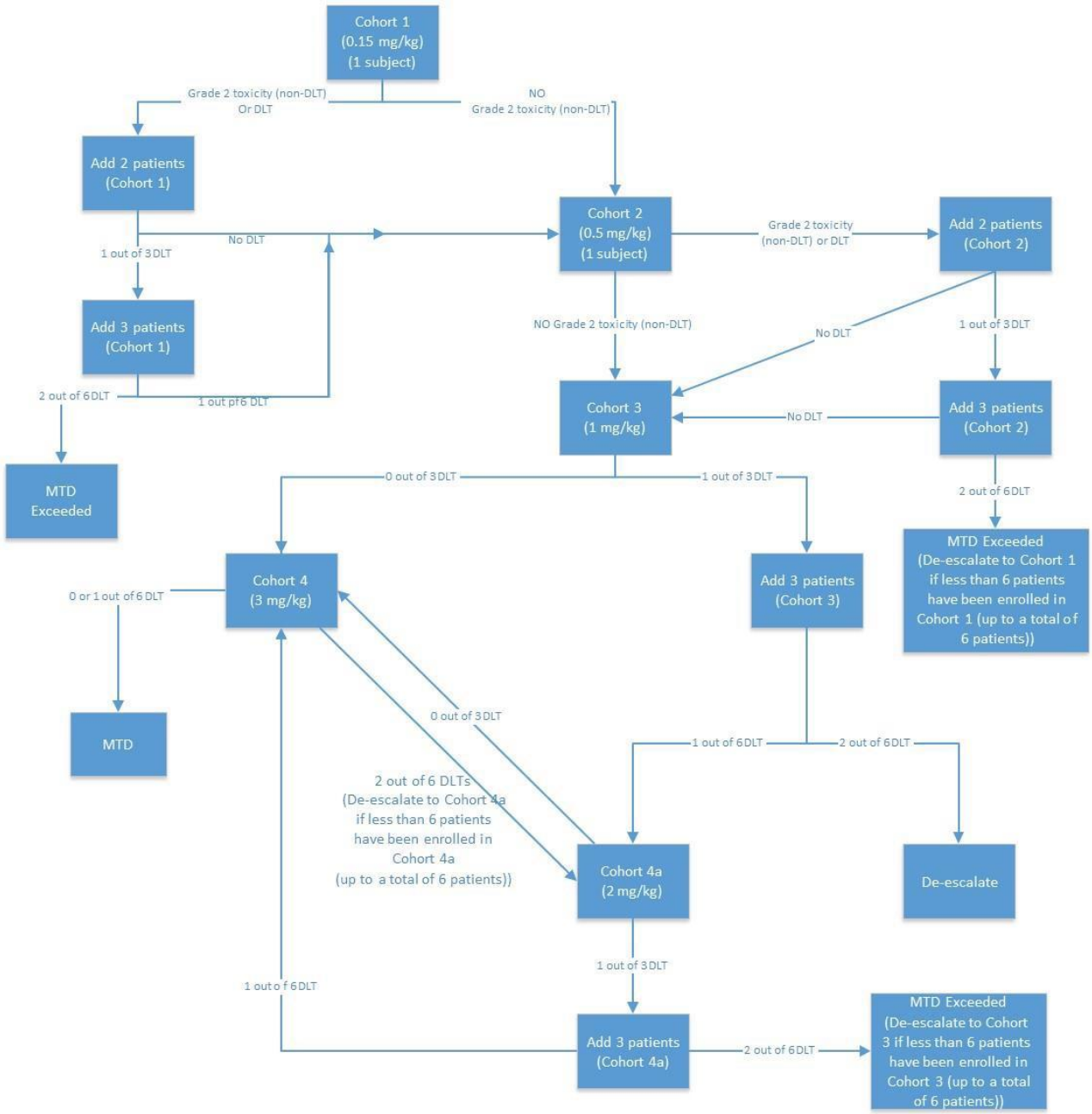
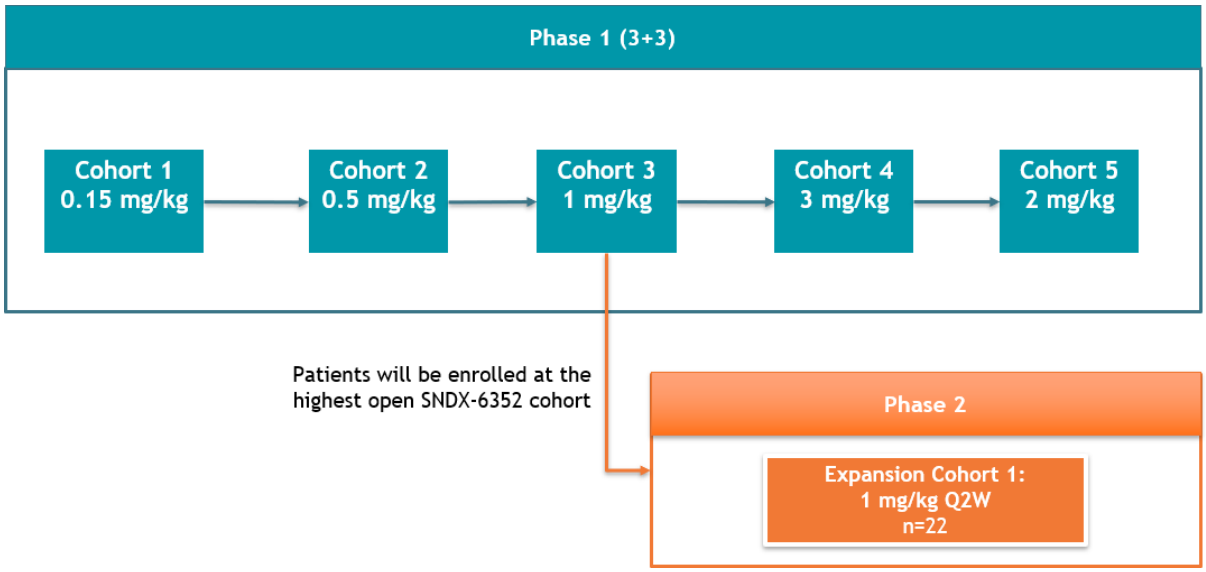


Figure 2: Phase 2 1 mg/kg Dose Expansion



4.2. Rationale for Study Design

Phase 1 is a modified dose escalation 3+3 design, which is a well-accepted design in cancer studies (Jaki, et al 2013). As a precautionary measure, the initial 2 cohorts (sub-optimal doses of SNDX-6352, 0.15 mg/kg and 0.5 mg/kg) are single subject cohorts, prior to starting with 1 mg/kg. The study also allows expediting dose escalation from 1 mg/kg to 3 mg/kg without compromising subject's safety. Intermediary doses may also be investigated, depending on outcome. For subjects who start with the 2 lower doses (0.15 mg/kg and 0.5 mg/kg), intra-subject dose escalation is allowed to enable them to benefit from a therapeutic dose. The dose levels, i.e., 0.15, 0.5, 1, 2 (if required), and 3 mg/kg, are expected to be sufficient for evaluation of the safety, PK and PD profile, OBD, and early indications of clinical activity. The PK and extent of target binding will be closely monitored during this clinical study.

Phase 2, dose expansion, is an open-label design, evaluating the 1 mg/kg dose in a larger sample size based on preliminary PK, PD, safety and preliminary evidence of clinical activity observed in Phase 1.

4.3. Justification for Dose

For Phase 1, the SNDX-6352 starting dose of 0.15 mg/kg is planned with ascending dose levels of 0.5, 1, 2 (if required), and 3 mg/kg. The starting dose of 0.15 mg/kg was selected based on available clinical data (PK and safety) in healthy volunteers (SNDX-6352-0001) and the preliminary data from the multiple ascending dose study SNDX-6352-0502 Phase 1a. This was determined by taking both the no-observed-adverse-effect-level (NOAEL) and minimum anticipated biological effect level (MABEL) for SNDX-6352 into consideration.

In SNDX-6352-0001, 3 cohorts of healthy volunteer subjects have received a single dose of either 0.15 mg/kg, 1 mg/kg, or 3 mg/kg and completed the PK sampling and safety assessments for each of those dose levels. Based on the data from the 1 mg/kg cohort, the average maximum concentrations were approximately 22500 ng/mL and were achieved by approximately 1 hour. The $AUC_{0\text{-last}}$ estimates (over 7 days) were determined to be 1289 µg/*hr/mL. The half-life of SNDX-6352 was determined to be approximately 56 hours. There were no DLTs that would prevent dosing the higher dose cohorts. Mild to moderate eyelid swelling lasting for up to approximately 4 weeks has been observed in the majority of subjects dosed at 3 mg/kg, which precluded further dose escalation in healthy volunteers.

SNDX-6352 PK and PD data from healthy subjects and solid tumor patients indicate that all doses tested at Q2W, ranging from 0.15 mg/kg to 6 mg/kg have demonstrated evidence of biologic activity. Measurement of circulating non-classical monocytes levels, CSF-1 and IL-34 levels and receptor occupancy indicate a dose dependent effect of SNDX-6352 on these markers that correlate well with drug concentrations. Increased dosing effects the magnitude of change as well as duration of effect. At 1 mg/kg in both healthy subjects and solid tumor patients, depletion of non-classical monocytes is prolonged through approximately Day 10 of a 14-day dosing interval with recovery to baseline by the next dose. Doses higher than 1 mg/kg deplete monocytes for the full 14-day interval.

Preliminary data from the Phase 1 portion of this study indicate that both the PK and monocyte depletion effects at 1mg/kg are consistent with the data from the prior studies demonstrating that dose dependent biologic activity is conserved across healthy subjects, solid tumor and cGVHD subjects. These data justify 1 mg/kg as a potential optimal biologic dose with early evidence of clinical benefit in cGVHD subjects treated at this dose level. The Phase 2 expansion phase will further evaluate preliminary efficacy of SNDX-6352 at 1 mg/kg in subjects with active cGVHD who have failed two prior therapies due to progression of disease, intolerability or toxicity. Up to 22 subjects are anticipated to participate.

Please refer to SNDX-6352 IB for more details. For dose modifications criteria, please refer to Section 6.7.

4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed post-study follow-up assessments which are at 90 days after termination of study intervention or the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last post-study assessment (90 days after the study intervention termination) of the last subject in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Subjects are eligible to be included in the study, in either Phase 1 or Phase 2, only if all the following criteria apply:

Age

1. Subject must be 6 years of age or older, at the time of signing the informed consent.

Type of Subject and Disease Characteristics

2. Subjects who are allogeneic HSCT recipients with cGVHD requiring systemic immune suppression.
3. Subjects with active cGVHD who have received at least 2 lines of therapy. Subjects ≥18 years of age with active cGVHD who have erythematous rash involving >25% body surface area or a NIH mouth score of >4 must have received prior ibrutinib therapy.

   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, et al 2015).
4. Subjects 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.

Diagnostics assessments

5. Karnofsky Performance Scale of ≥60 with a life expectancy of at least 3 months (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 enrollment as follows:
   a. Absolute neutrophil count ≥1.5 × 10^9/L without growth factors within 1 week of study entry);
   b. Platelet count ≥50 × 10^9/L (without transfusion within 2 weeks of study entry);
   c. Total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ upper limit of normal (ULN);
   d. For subjects with suspected liver cGVHD, ALT and AST ≤3 × ULN and total bilirubin ≤ULN;
   e. Creatinine clearance (CrCl) ≥50 mL/min/1.73 m^2 or a serum creatinine ≤1.5 mg/dL based on the Cockcroft-Gault formula.

Sex

7. Male and/or female.

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

8. Male subjects: Non-sterilized male subjects 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 subjects should refrain from sperm donation throughout this period.
9. Female subjects: Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal subjects. 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:
    - 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 subjects of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (Table 14) 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. Non-sterilized male partners of a female subject 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 subjects should also refrain from breastfeeding throughout this period.

Informed Consent

10. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.2) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Subjects are excluded from the study, in both Phase 1 and Phase 2, 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 or other evidence of severe illness, uncontrolled infection or any other conditions that would make the subject, in the opinion of the Investigator, unsuitable for the study
4. Known history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or hepatitis B virus (HBV).
5. Diagnosed with another malignancy (other than malignancy for which transplant was performed) within 3 years of enrollment, unless previously treated with curative intent and must be approved by Sponsor medical monitor (e.g., 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).
6. Female subjects who is pregnant or breastfeeding.

Prior/Concomitant Therapy

7. Previous exposure to study intervention or known allergy/sensitivity to study intervention.
8. Taking agents other than a corticosteroid and one calcineurin inhibitor (CNI) for treatment of cGVHD (This does not include agents being prescribed expressly for the treatment of acute GVHD).

   To be eligible, at study enrollment, subjects must have been on stable dose of corticosteroids and CNI for at least 2 weeks.

   For approved or commonly used agents, a washout of 2 weeks or 5 half-lives, whichever is shorter, is required at study enrollment.

Prior/Concurrent Clinical Study Experience

9. Receiving an investigational treatment within 28 days of study entry.

5.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) maybe rescreened. Rescreened subjects should be assigned the same subject number as for the initial 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 subject according to the study protocol.

6.1. Study Intervention(s) Administered

Table 2: Study Intervention

Intervention Name	SNDX-6352
Type	Biologic
Dose Formulation	Solution for infusion
Unit Dose Strength(s)	mg/kg
Dosage Level(s)	0.15, 0.5, 1, 3, 2 mg/kg and other intermediary doses and/or alternative dosing schedules based on emerging data. Frequency: Every 2 weeks (Day 1 and 15 of each 4-week cycle) up to 6 months, if no progression, either Q2W or Q4W up to Month 12, at the Investigator's discretion in discussion with the Sponsor.
Route of Administration	IV infusion over 30 minutes; time windows of -5 minutes to +10 minutes are permitted (i.e., infusion time is 25 to 40 minutes). The exact duration of infusion should be recorded in both source documents and eCRFs.
IMP definition	A new drug or biological drug that is used in a clinical investigation (FDA)
Sourcing	SNDX-6352 is manufactured by Nova Laboratories Ltd (Leicestershire UK) for UCB Pharma S.A. (Braine-l'Alleud Belgium). Study intervention will be provided to the site centrally by the Sponsor or designated representative.
Packaging and Labeling	SNDX-6352 is supplied as a 1.3 mL (1.0 mL extractable volume) sterile, preservative free solution in 2 mL, colorless, Type I glass vials closed with a rubber stopper and sealed with an aluminum overseal and flip-off cap. The vials are single use only and contain no preservatives. Label text for the SNDX-6352 vial will at a minimum include the protocol number, the contents of the vial (e.g., SNDX-6352 50 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

6.2. 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 subjects 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 50 mL with 0.9% saline solution (sodium chloride injection) 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 subject's weight in kilograms (kg). All subjects should be weighed within 3 days prior to dosing. If the subject 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.
5. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
6. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable. The study is open-label.

6.4. Study Intervention Compliance

Administration of SNDX-6352 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 subject 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.

A mandatory 2-hour observation period after each SNDX-6352 infusion (for potential infusion-related reactions) is required following the first 4 SNDX-6352 infusions. If no infusion reaction occurs in relation to the first 4 infusions, the post-infusion observation period may be discontinued at investigator's discretion. Patients who experience an infusion-related reaction at any point must continue to undergo the mandatory observation after each infusion.

6.5. Dose Limiting Toxicity Criteria

DLTs will be assessed during a DLT assessment window, which is the first 28 days from the first dose of SNDX-6352 or administration of the third dose (C2D1), whichever is later (from C1D1 to C2D1). All DLTs will be reported in the Sponsor's electronic data capture (EDC) system within 24 hours.

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value that occurs within the DLT assessment window (defined above), meets any of the criteria below, is assessed by the Investigator as not being definitely attributable to underlying disease, disease progression, inter-current illness, concomitant medications or any other alternative cause.

Hematological toxicities

- Neutropenia
  - Grade 4 neutropenia (absolute neutrophil count [ANC] <500/µL)
  - Any grade febrile neutropenia [i.e., ANC <1000 per mm^3 and associated with fever (oral temperature ≥38ºC) requiring antibiotic therapy]
- Thrombocytopenia
  - Grade 4 thrombocytopenia (i.e., platelet <25,000 per mm^3)
  - Grade 3 thrombocytopenia (i.e., platelets <50,000 per mm^3) with clinically significant bleeding
- Grade 4 anemia

Non-hematological toxicities:

- Any Grade 3 or Grade 4 non-hematological, non-hepatic toxicity
- Criteria meeting Hy's Law: elevation of ALT/AST ≥3 × ULN and concurrent total bilirubin ≥2 × ULN in the absence of cholestasis (elevation of alkaline phosphatase (ALP) and GGT > 2.5 × ULN)
- ≥ Grade 3 ALT/AST elevation
- Isolated Grade ≥2 ALT or AST (> 3 to 5 × ULN) in the absence of cholestasis (elevation of ALP and gamma glutamyl transferase (GGT) > 2.5 × ULN).

  Exceptions:

  - Asymptomatic Grade 2 AST (> 3 to 5 × ULN) that is accompanied by ≤ Grade 1 ALT (> ULN to 3 × ULN) and ≤ Grade 1 total bilirubin (> ULN to 1.5 × ULN), will not be considered DLT
- For Q4W dosing only, any asymptomatic ≥Grade 3 lipase or amylase if there is end organ damage or if it lasts for ≥4 weeks.

- ≥ Grade 3 creatine kinase (CK) increase with clinical symptoms and/or evidence of end organ damage (i.e., increased serum or urine myoglobin)

  Exception:

  - In the absence of any clinical symptoms and no evidence of end organ damage, ≥ Grade 3 will NOT be considered a DLT (subjects will undergo an assessment for end organ damage to exclude the possibility of toxicity)

- Other Grade 3 laboratories abnormalities

  Exception:

  - Isolated Grade 3 electrolyte abnormalities persisting for >72 hours despite maximal medical intervention will be considered a DLT unless they are considered to be part of a syndrome in which the grading of the syndrome would itself determine whether the finding was a DLT

- Grade 3 infusion reaction
- ≥ Grade 3 periorbital edema
- Subjects who require delay in therapy for ≥2 weeks for any CTCAE grade toxicity during the DLT assessment period. Additionally, toxicity resulting in subject receiving < 70% of planned dose intensity within the first 6 weeks; note the 6-week time frame accounts for dose delays with the intention being to dose at least 3 times within 6 weeks including C2D1.

Subjects who receive <90% of the SNDX-6352 infusion in Cycle 1 (i.e., because the infusion had to be discontinued due to an infusion reaction) and do not experience a DLT will not be considered evaluable in the assessment of the overall DLT rate for the particular dose level cohort and will be replaced.

Subjects who withdraw or are withdrawn from study treatment prior to completing the DLT assessment window for any reason other than a study intervention-related toxicity through Cycle 1, will not be considered evaluable for DLTs and will be replaced.

If a subject experiences a DLT in Cycle 1, the study intervention will be held until recovery to Grade 1 or baseline, and if the Investigator considers it in the subject's best interest to continue on study treatment, with the approval by the Sponsor medical monitor, study intervention administration may be resumed at a reduced dose.

6.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment 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

All treatments that the Investigator considers necessary for a subject's plan of care may be administered concomitantly with SNDX-6352 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 and fungal infections) are permitted per institutional policy.

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

6.6.1. Prohibited Medications

- Only 1 systemic corticosteroid and 1 CNI are allowed at the time of enrollment; any other immune suppressive agents for treatment of chronic GVHD are not permitted.
  - This does not include agents for treatment of acute GVHD and prophylaxis for chronic GVHD.
  - At study enrollment, subjects must have been on stable dose of corticosteroids for at least 2 weeks.
  - Corticosteroids may be tapered, per local institutional guidelines, after the first 4 weeks of study intervention administration at the discretion of the Investigator. One re-escalation of corticosteroids (up to a dose of 1 mg/kg daily of prednisone or equivalent) up to 5 months from start of SNDX-6352 is allowed at the discretion of Investigator.
- Live virus vaccinations
- Antineoplastic systemic chemotherapy or biological therapy except when used as maintenance therapy (e.g., FLT3 inhibitors or TKIs started prior to enrollment into this study) to prevent relapse.
- Investigational agents other than SNDX-6352
- Radiation therapy: Administration of palliative radiation therapy will be considered relapse or progression of the primary disease.
- Traditional herbal medicines: these therapies are not fully studied, and it is unknown whether their use may result in unanticipated drug-drug-interactions that may cause or confound the assessment of toxicity.

6.7. Dose Modification

For the first 3 doses, dose delays, but not dose reduction, will be allowed for SNDX-6352. Any dose delay or modification during the first 2 cycles in Phase 1 should be discussed with the Sponsor's Medical Monitor.

In subjects who have a DLT-type AE (Section 6.5), study intervention treatment will be held until resolution of toxicity to Grade 0-1.

After the first 3 doses, both dose delays and dose reductions will be allowed as described below. Subjects who do not tolerate therapy after 1 dose level reduction from starting dose must withdraw from the study. Once the SNDX-6352 dose is reduced, it cannot be re-escalated. 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 based on toxicity described in the sections below and should be properly documented in source documents. Investigators may take a more conservative approach than the guidelines outlined in the protocol on the basis of clinical judgment that is in the best interest of the subject. Such instances should be reported to the Medical Monitor.

6.7.1. Axatilimab Taper

If after 12 months of treatment, axatilimab treatment is to be stopped, an axatilimab taper followed by discontinuation may be pursued as an alternative to immediate agent discontinuation. Table 3 provides dose taper guidance.

Table 3: Axatilimab Taper Schedule and Duration for Each Dose Level

Last dose administered	**Taper 1 (8 weeks)**	**Taper 2 (8 weeks)**	**Taper 3 (8 weeks)**	**Taper 4 (8 weeks)**	
3 mg/kg Q2W	3 mg/kg Q4W (2 doses)	2 mg/kg Q4W (2 doses)	1 mg/kg Q4W (2 doses)	1 mg/kg Q8W (1 dose)	**End**
3 mg/kg Q4W	2 mg/kg Q4W (2 doses)	1 mg/kg Q4W (2 doses)	1 mg/kg Q8W (1 dose)	**End**	
2 mg/kg Q4W	1 mg/kg Q4W (2 doses)	1 mg/kg Q8W (1 dose)	**End**		
1 mg/kg Q2W	1 mg/kg Q4W (2 doses)	1 mg/kg Q8W (1 dose)	**End**		

Q2W = every 2 weeks; Q4W = every 4 weeks

For doses not listed, consultation with the Sponsor is required before taper initiation.

Patients completing the taper schedule will continue undergoing study-specific assessment every 28 days, with the final treatment period evaluation occurring 28 days after the last dose. Thirty (± 7) days after the last evaluation in the treatment period, patients will initiate the Safety Follow-up period of the study.

Should progression of cGVHD be recorded at any point after taper initiation, axatilimab use on the protocol may not be restarted.

6.7.2. Guidelines for Toxicity Management

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

6.7.2.1. AST, ALT, Bilirubin, CK, Amylase and Lipase elevation

Dose modification guidelines for SNDX-6352 due to AST, ALT, bilirubin, CK, amylase or lipase elevation are specified in Table 4.

Table 4: AST, ALT Bilirubin, CK, Amylase and Lipase: Dose Modification Guidelines for SNDX-6352

Toxicity	Dose modifications
Asymptomatic Grade 2 AST (>3 to 5 × ULN), with ≤Grade 1 ALT and ≤Grade 1 total bilirubin, no change from baseline of ALT and total bilirubin	Continue SNDX-6352 without dose delay or reduction with agreement from both Investigator and Sponsor Medical Monitor
Grade 2 ALT (>3 to 5 × ULN) with total bilirubin ≤Grade 1	Hold SNDX-6352 dose until recovery to Grade 1 (> ULN to 3 × ULN) or baseline, then resume SNDX-6352 at the same dose
Grade 3 AST or ALT (> 5 to 20 × ULN) with total bilirubin ≤Grade 1	Hold SNDX-6352 dose until recovery to Grade 1 (> ULN to 3 × ULN) or baseline, then resume SNDX-6352 at a reduced dose (if this will be the 4th planned dose or onward)
Concurrent ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN in the absence of cholestasis (elevation of ALP and gamma glutamyl transferase (GGT) >2.5 × ULN)	Permanently discontinue SNDX-6352
Grade 4 AST or ALT (>20 × ULN)	Permanently discontinue SNDX-6352
Grade 2 total bilirubin	Hold SNDX-6352 dose, rule out hemolysis and cholestasis, until recovery to Grade 1 or baseline, then resume SNDX-6352 at the same dose
Grade 3 total bilirubin	Hold SNDX-6352 dose, rule out hemolysis and cholestasis, until recovery to Grade 1 or baseline, then resume SNDX-6352 at a reduced dose (if this will be the 4th planned dose or onward)
≥ Grade 3 CK, amylase or lipase in the absence of any clinical symptoms	• Before administering axatilimab, conduct diagnostic evaluation, eg, serum and urine myoglobin, or CPK-MB, BUN, creatinine, ECG, troponin (I or T). • If results show no evidence of end organ damage, continue axatilimab without dose reduction, with agreement from both Investigator and Sponsor Medical Monitor. If the results show evidence of end organ damage, axatilimab should be discontinued.
Symptomatic Grade 3 CK, amylase or lipase	Permanently discontinue SNDX-6352 with agreement from both Investigator and Sponsor Medical Monitor
SNDX-6352 can cause modulation of Kupffer cells in the liver, which may lead to elevation of liver enzymes (ALT and AST). Serum bilirubin, alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) will need to be monitored along with ALT and AST for assessment of liver toxicity.	

6.7.2.2. Other Non-hematologic Toxicity

The rules for the management of other non-hematologic toxicities are outlined as follows in Table 5 with toxicities graded by the Investigator according to the NCI CTCAE, version 5.0.

Table 5: Other Non-hematologic Toxicity: Dose Modification Guidelines for SNDX-6352

Toxicity	Dose modifications
Grade 4	Administer symptomatic remedies/start prophylaxis. Any Grade 4 events require permanent treatment discontinuation from SNDX-6352.
Grade 3	Administer symptomatic remedies/ start prophylaxis. Hold SNDX-6352 dose until recovery to Grade 1 or baseline under the following directions: 1. If recovered within 4 weeks, resume SNDX-6352 at a reduced dose (if this will be the 4th dose or onward). 2. If the SNDX-6352 dose is held for more than 4 consecutive weeks, permanently discontinue SNDX-6352.
Grade 2	Administer symptomatic remedies / start prophylaxis. Hold SNDX-6352 dose until recovery to Grade 1 or baseline, resume SNDX-6352 at the same dose.

6.7.2.3. Hematologic Toxicity

The guidelines in Table 6 will be followed for determining the dose modifications based on hematologic status at the time of planned dosing.

Table 6: Hematologic Toxicity: Dose Modification Guidelines for SNDX-6352

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 SNDX-6352 dose until recovery to Grade 1 or study baseline under the following directions. 1. If recovered within 4 weeks, resume SNDX-6352 at next lower dose (if this will be the 4th dose or onward) 2. If the SNDX-6352 dose is held for more than 4 consecutive weeks, permanently discontinue SNDX-6352.
Recurrence of the same hematologic toxicity	If the **same** hematologic toxicity **recurs**: 1. Administer symptomatic remedies/ start prophylaxis. Hold SNDX-6352 dose until recovery to Grade 1 or baseline. 2. If recovered within 7 days, resume SNDX-6352 at next lower dose. 3. If the episode is not recovered within 14 days despite SNDX-6352 dose reduction to next lower dose, as described above, permanently discontinue SNDX-6352. 4. If the 3rd episode, permanently discontinue SNDX-6352.

6.7.2.4. SNDX-6352 Infusion-Related Reaction

If a subject experiences an SNDX-6352 infusion-related reaction, they may continue on study intervention treatment per guidance presented in Table 7. Subjects who previously experienced an infusion-related reaction will receive a premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol approximately 30 to 60 minutes prior to each subsequent dose of SNDX-6352.

Treatment modifications for SNDX-6352 infusion-related reactions are outlined in Table 7.

Table 7: Infusion-related Reactions for SNDX-6352

NCI-CTCAE Grade	Treatment Modification for SNDX-6352
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease SNDX-6352 infusion rate by 50% being given at the time of event onset and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drug [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Temporarily discontinue SNDX-6352 infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity and monitor closely for any worsening. At next cycle, administer oral premedication with antihistamine and anti-pyretic and monitor closely for infusion reaction.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: Life-threatening consequences – urgent intervention is indicated.	Stop the SNDX-6352 infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from SNDX-6352 treatment and must not receive any further SNDX-6352 treatment.
NSAIDs = nonsteroidal anti-inflammatory drugs	

If a Grade 2 infusion-related reaction does not improve or worsens after implementation of the modifications indicated in Table 7 (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 subject 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 subject removed from SNDX-6352 treatment.

6.7.2.5. Immune-related Adverse Events for SNDX-6352

Because inhibition of CSF-1/IL-34 signaling pathway may stimulate the immune system, immune-related adverse events (irAEs) may occur. General guidance includes the following:

- Grades 1 to 2: Treat symptomatically or with moderate dose steroids, more frequent monitoring.
- Grades 1 to 2 (persistent for >5-7 days): Manage similarly to high-grade adverse events (Grades 3 to 4).
- Grades 3 to 4: Treat with high-dose corticosteroids.

Please refer to Table 8 for management of irAEs.

Table 8: Management of Immune-related Adverse Events for SNDX-6352

Gastrointestinal Immune-related Adverse Events		
Severity of Diarrhea/Colitis (NCI CTCAE v5.0)	**Management***	**Follow-up***
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	Continue SNDX-6352 therapy with symptomatic treatment (e.g., loperamide) after ruling out infectious etiology.	Close monitoring for worsening symptoms. Educate subject to report worsening immediately. If worsens, treat as Grade 2 or Grade 3 to 4.
Grade 2 Diarrhea: 4 to 6 stools/day over baseline; IV fluids indicated < 24 hours; not interfering with activity of daily living (ADL) Colitis: abdominal pain; blood in stool	Delay SNDX-6352 therapy; symptomatic treatment. Consider lower GI endoscopy and biopsy to evaluate for acute GVHD	If improves to Grade 1, resume SNDX-6352 therapy. If persists > 5 to 7 days or recurs, give 0.5 to 1.0 mg/kg/day oral methyl-prednisolone or equivalent. When symptoms improve to Grade 1, taper steroids over at least 1 month, and resume SNDX-6352 therapy per protocol. If worsens or persists > 3 to 5 days with oral steroids, treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools/day over baseline; incontinence; IV fluids ≥ 24 hours; interfering with ADL. Colitis (Grade 3): severe abdominal pain; medical intervention indicated; peritoneal signs Grade 4: life-threatening, perforation	Discontinue SNDX-6352 therapy per protocol; give 1 to 2 mg/kg/day methylprednisolone IV or equivalent. Consider lower GI endoscopy and biopsy to evaluate for acute GVHD	If improves, continue steroids until Grade 1, then taper over at least 1 month. If persists > 3 to 5 days, or recurs after improvement, add infliximab 5 mg/kg (if no contra-indication). Note: Infliximab should not be used in cases of perforation or sepsis.

Dermatological Immune-related Adverse Events		
Grade of Rash (NCI CTCAE v5.0)	**Management***	**Follow-up***
Grades 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids). Continue SNDX-6352 therapy.	If persists > 1 to 2 weeks or recurs: consider skin biopsy; delay SNDX-6352 therapy. Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, and resume SNDX-6352 therapy. If worsens, treat as Grade 3 to 4.
Grades 3 to 4 Covering >30% body surface area; life-threatening consequences	Delay or discontinue SNDX-6352 therapy; consider skin biopsy and dermatology consult; give 1.0 to 2.0 mg/kg/day methyl-prednisolone IV or IV equivalent.	If improves to Grade 1, taper steroids over at least 1 month. Resume SNDX-6352 therapy.
Pulmonary Immune-related Adverse Events		
Grade of pneumonitis (NCI CTCAE v5.0)	**Management***	**Follow-up***
Grade 1 Radiographic changes only	Consider delay of SNDX-6352 therapy; monitor for symptoms every 2 to 3 days; consider Pulmonary and Infectious Disease consults.	Re-image at least every 3 weeks. If worsens, treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Delay SNDX-6352 therapy; Pulmonary and Infectious Disease consults; monitor symptoms daily, consider hospitalization; give 1.0 mg/kg/day methylprednisolone IV or oral equivalent; consider bronchoscopy, lung biopsy.	Re-image every 1 to 3 days. If improves, when symptoms return to near baseline, taper steroids over at least 1 month, then resume SNDX-6352 therapy. If not improving after 2 weeks or worsening, treat as Grade 3 to 4.
Grades 3 to 4 Severe new symptoms; New or worsening hypoxia; life-threatening	Discontinue SNDX-6352 therapy; hospitalize; Pulmonary and Infectious Disease consults; give 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent. Consider bronchoscopy, lung biopsy.	If improves to baseline, taper steroids over at least 6 weeks. If not improving after 48 hours or worsening, add additional immunosuppression (e.g., infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).

Hepatic Immune-related Adverse Events		
Grade of liver test elevation (NCI CTCAE v5.0)	**Management***	**Follow-up***
Grade 2 Total bilirubin >1.5 to ≤3 × ULN	Delay SNDX-6352 therapy; increase frequency of monitoring to every 3 days.	If returns to baseline, resume routine monitoring; resume SNDX-6352 therapy. If elevations persist > 5 to 7 days or worsen, give 0.5 to 1 mg/kg/day methyl-prednisolone or oral equivalent. When liver function test (LFT) returns to Grade 1 or baseline, taper steroids over at least 1 month. Resume SNDX-6352 therapy.
Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN	Discontinue SNDX-6352 therapy; increase frequency of monitoring to every 1 to 2 days. Give 1.0 to 2.0 mg/kg/day methyl-prednisolone IV or IV equivalent. Consult gastroenterologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade 2, taper steroids over at least 1 month. If does not improve in > 3 to 5 days, worsens or rebounds, add mycophenolate mofetil 1 g twice daily. If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
AST or ALT >5 × ULN with total bilirubin ≤1.5 × ULN	Delay SNDX-6352 therapy; increase frequency of monitoring to every 1 to 2 days. Give 1.0 to 2.0 mg/kg/day methyl-prednisolone IV or IV equivalent. Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	Asymptomatic; delay dose until resolves to Grade ≤ 1, then resume SNDX-6352 at a reduced dose (if this will be the 4th planned dose or onward)
Exception: Asymptomatic, isolated Grade 2 AST with Grade 1 ALT and TB)	Continue study treatment without dose delay or reduction with agreement from both Investigator and Sponsor medical monitor	Symptomatic; hold dose until resolves to Grade ≤ 1, permanently discontinue SNDX-6352 dosing.

Endocrine Immune-related Adverse Event		
Endocrine Disorder	**Management***	**Follow-up***
Asymptomatic TSH abnormality	Continue SNDX-6352 therapy. If TSH < 0.5 × LLN, or TSH > 2 × ULN, or consistently out of range in 2 subsequent measurements, include T4 at subsequent cycles as clinically indicated. Consider endocrinology consult.	
Symptomatic endocrinopathy	Evaluate endocrine function. Consider pituitary scan. If symptomatic with abnormal lab/pituitary scan, delay SNDX-6352 therapy; give 1 to 2 mg/kg/day methyl-prednisolone IV or oral equivalent. Initiate appropriate hormone therapy. If no abnormal lab/pituitary MRI scan but symptoms persist, repeat labs in 1 to 3 weeks/MRI in 1 month.	If improves (with or without hormone replacement), taper steroids over at least 1 month. Resume SNDX-6352 therapy. Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component.
Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue SNDX-6352 therapy; rule out sepsis. Stress dose of IV steroids with mineralocorticoid activity; give IV fluids. Consult endocrinologist. If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy.	

* A delay of SNDX-6352 for up to 6 weeks from the day they were scheduled to receive their next dose is acceptable for subjects who are actively receiving steroid treatment for the management of immune-related adverse events

6.8. Intervention after the End of the Study

No formal open-label extension is planned after the end of the study (12 months of treatment).

Subjects who are deriving benefit may be allowed to continue at present or reduced dose based on Investigator's discretion and in consultation with the Sponsor.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a subject 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 subject 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).

7.1.1. Temporary Discontinuation

See Section 6.7 for dose modification and toxicity management.

7.2. Subject Discontinuation/Withdrawal from the Study

Subjects 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 subject does not wish to take study intervention any longer but is still willing to collaborate in providing further data by continuing on study (e.g., participate in all subsequent study visits or procedures or follow-up contact). Full withdrawal of consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to, or is unable to, continue further study participation. Any subject 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 protocol-required all tests and evaluations listed for the End of Treatment visit and Safety Follow-up visits. If a subject fails to return for the necessary visits, every effort must be made to contact the subject 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 subject 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 subject'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 subject 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 subject fails to return to the clinic for a required study visit:

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

- Study procedures and their timing for Phase 1 and Phase 2 are summarized in the Phase 1 SoA (Section 1.2). Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each subject over the duration of the study (12 treatment cycles), including any extra assessments that may be required, will not exceed 200 mL (~14 tablespoons). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.2).

8.1.1. 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.

8.1.2. 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.

Investigators will be instructed to counsel subjects not to operate or drive heavy, complex machinery until 30 days after the last dose of SNDX-6352.

8.1.3. Vital Signs

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

8.1.4. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.2 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals).
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- ECGs will be recorded after the subject 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.
- An ECG may be repeated anytime, as clinically indicated.

8.1.5. Karnofsky/Lansky Performance Status Scale

The Karnofsky/Lansky Performance Status allows subjects 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 subjects. The Karnofsky Scale is designed for subjects aged 16 years and older, and the Lansky Scale is designed for subjects less than 16 years old (Lansky, et al 1987). The Karnofsky scale is widely used validated tool in oncology settings, especially HSCT (Crooks, et al 1991; O'Toole and Golden 1991; Schag, et al 1984).

The Karnofsky/Lansky performance status scales is presented in Table 9.

Table 9: Karnofsky and Lansky Performance Status

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

8.1.6. Clinical Safety Laboratory Assessments

- See Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and see 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 subject'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.
  - All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.2).

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.

8.2.1. Response Determination according to 2014 NIH Consensus definitions

Response evaluation will be an exploratory endpoint in Phase 1 and the primary endpoint in Phase 2. Overall physician-assessed responses will be evaluated at C7D1 as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical trials in cGVHD (Lee, et al 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 10 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 10: 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
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

ULN = upper limit of normal.
Source: (Lee, et al 2015)

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

Physician-reported global and organ specific cGVHD activity assessment is an exploratory endpoint in Phase 1 and a secondary endpoint in Phase 2.

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 10.5.1). The clinicians will provide a subjective assessment of current overall chronic GVHD severity on a 4-point scale (no chronic GVHD, mild, moderate, severe) independent of the recorded NIH global severity score (Table 10, last line), and their evaluations of cGVHD changes since the last assessment scored on a 7-point scale. Key organ assessments include skin, mouth, liver, upper and lower GI, esophagus, lung, eye, and joint/fascia (Jagasia, et al 2015; Lee, et al 2015).

8.2.3. Patient-Reported cGVHD Activity Assessment

Patient-reported cGVHD activity assessment (Section 10.5.2) is an exploratory endpoint in Phase 1 and a secondary endpoint in Phase 2.

Changes in patient-reported symptom activity will be evaluated using the cGVHD Lee symptom scale (Lee, et al 2002).which has been recommended for use by the 2005 and 2014 National Institutes of Health (NIH) Consensus Conferences to capture cGVHD symptoms.

The Lee cGVHD symptom questionnaire asks subjects 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, et al 2002). Published evidence supports its validity, reliability, and sensitivity to cGVHD severity (Lee, et al 2015; Merkel, et al 2016).

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 subject (or, when appropriate, by a caregiver, surrogate, or the subject'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 subject to discontinue the study intervention and/or the study (see Section 7).

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

All AEs and SAEs will be collected at the time points specified in the SoA (Section 1.2).

Table 11 below 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 intervention
Reporting period	From consent until 30 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	Within 24 hours

Medical occurrences that begin before the start of study intervention 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 subjects are properly captured in the subject'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 subject has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

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 subject 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 subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 10.3.3), will be followed until resolution, stabilization, the event is otherwise explained, or the subject 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).

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 subject 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 (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female subjects, and female partners of a male subject, 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 subjects, and female partners of male subjects, becoming pregnant must be followed to completion/termination of the pregnancy.
- Abnormal pregnancy outcomes (e.g., 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 subjects 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 eCRF as an AE 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 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 eCRF page in the subject's CRF within the appropriate time frame.

In addition, the following will not be considered AEs

- Worsening of a pre-existing medical condition, (i.e., 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.
- Interventions for pretreatment conditions (i.e., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered AEs.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- *The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject.*

  OR

- *The Investigator considers that there is a reasonable possibility that the event was related to study intervention.*

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 exceeding the dose prescribed in the protocol by 20%. 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 subject 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 subject.

8.5. Pharmacokinetics

- Whole blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of SNDX-6352 as specified in the SoA (Section 1.2). Instructions for the collection and handling of biological samples will be provided by

the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

- Samples will be used to evaluate the PK of SNDX-6352. Samples collected for analyses of SNDX-6352 serum concentration may also be used to evaluate safety, efficacy and/or pharmacodynamic aspects related to concerns or questions arising during or after the study.
- Any genetic analyses performed on these serum samples will be consistent with consent given for the skin punch biopsy. Subject confidentiality will be maintained. At visits during which blood samples for the determination of PK, ADA and PD related to SNDX-6352 will be taken, 1 sample of sufficient volume can be used.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.6. Pharmacodynamics and Exploratory endpoints

[redacted]

8.7. Biomarkers

Collection of samples for other biomarker research is also part of this study. The following blood samples for immune correlate analyses biomarker research may be performed and will be collected from all subjects in this study as specified in the SoA (Section 1.2):

- Levels of blood immune parameters that may include CSF-1, IL-34, IFN-gamma, IL-1beta, IL-2, IL-4, IL-5, IL-6, CXCL8/IL-8, IL-10, IL-12 (p70), IL-13, TNF-alpha, and sCD163, CD204/206 and change from baseline compared to PK, safety endpoints.
- Levels of Circulating classical and non-classical monocytes and change from baseline compared to PK, safety endpoints.
- Analysis of numbers of circulating immune cell subsets including CD8+ T cells, CD4+ T cells, B cells, natural killer (NK) cells and change from baseline compared to PK and safety endpoints.

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

Samples will be tested for SNDX-6352 related activities to evaluate their association with the observed clinical responses.

- In addition, samples will be stored, and analysis may be performed on biomarker variants thought to play a role in immune-modulation including, but not limited to, emergent candidate genes/genome-wide analysis for RNA, serum analytes, or tissue biomarkers to evaluate their association with observed clinical responses to SNDX-6352.
- 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 SNDX-6352.

Samples may be stored for a maximum of 10 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to SNDX-6352.

8.7.1. Immunogenicity Assessments

Antibodies to SNDX-6352 will be evaluated in serum samples collected from all subjects according to the SoA. Additionally, serum samples should also be collected at the final visit from subjects who discontinued SNDX-6352 or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to SNDX-6352 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to SNDX-6352 and/or further characterize the immunogenicity of SNDX-6352.

The detection and characterization of antibodies to SNDX-6352 will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to SNDX-6352 will also have matching samples evaluated for SNDX-6352 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 10 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to SNDX-6352.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

In Phase 1, statistical analyses will be descriptive and graphical in nature and no formal hypothesis testing will be performed.

Assuming a true DLT rate of 5% or less, there would be a 3% chance that dose escalation would be halted in a given cohort (i.e., observing 2 or more patients with DLT). If a true DLT rate of 50% is assumed, then there would be an 83% chance that dose escalation would be halted in a given cohort. It is anticipated that approximately 30 evaluable patients will be enrolled.

9.2. Sample Size Determination

Phase 1 Dose Escalation: Up to 30 subjects will be enrolled in this study.

Phase 2 Dose Expansion: A maximum of 22 subjects will be enrolled. A true ORR of 60% is hypothesized. A response rate greater than 30% is considered the lower threshold. The number of responders needed to declare the study a success was based on single proportion binomial test with 91% power and 1-sided significance level of 5%. Ninety percent 2-sided confidence interval of the observed one sample proportion will be calculated. The trial will be considered a success if the lower limit of 90% confidence interval is greater than 30%. Eleven responders out of 22 subjects will provide the lower limit of 90% confidence interval of 31.1% (90% CI [31.1%, 68.9%]).

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled (intent to treat [ITT] set)	All subjects who sign the ICF and were enrolled into the study.
Evaluable	Subjects who have received at least 1 cycle of treatment and have at least one post-baseline response assessment.
Full analysis set (FAS)	The FAS is a subset of all enrolled subjects, with subjects excluded for the following reasons: • Failure to receive at least one dose of SNDX-6352 • Lack of baseline data for those analyses that require baseline data
Safety set	All subjects who received at least 1 dose of study intervention.
PK/PD set	All subjects who received SNDX-6352 and who have evaluable PK /PD serum samples available at baseline and during at least 2 cycles of treatment. For skin biopsy and lung biopsy specimens, subjects with baseline and after 2 cycles will be evaluated.

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the subject 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 of the primary and secondary endpoints.

The analysis of safety will be performed on the Safety set while efficacy evaluation will be performed on the ITT, FAS, Evaluable set.

9.4.1. OBD Analyses: Phase 1

OBD will be determined after a review of the safety, tolerability, depletion of circulating non-classical monocytes and increasing concentrations of circulating CSF-1. The OBD is defined as the lowest safe dose with the highest rate of biologic activity. Biologic activity is determined by 100% reduction of non-classical monocytes at the time of dose interval and plateaued increase of circulating CSF-1 levels that persist for an entire dosing level.

9.4.2. Safety Analyses: Phase 1 and Phase 2

Safety will be assessed by clinical review of all relevant parameters including vital signs measurements, Karnofsky/Lansky performance scale, AEs, SAEs, physical and neurological examination findings, ECG results, and laboratory values.

Summary tables and listings will be provided for all reported treatment-emergent adverse events (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 number and percentage of patients experiencing the event by MedDRA system organ class and preferred term. In the event 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:

- DLTs
- All treatment-emergent adverse events
- Treatment-emergent adverse events by relationship to study drug treatment and maximum severity grade
- Treatment-emergent adverse events with action of study drug treatment delayed/interrupted or dose reduced
- Treatment-emergent adverse events with action of study treatment discontinued
- SAEs
- Neurological examination
- Changes in Karnofsky/Lansky performance status scale
- Changes in chemistry and hematology parameters
- Changes in vital signs, weight and ECGs

The observed DLT rate in each dose cohort will be calculated by the crude proportion of patients who experienced DLT with a 2-sided 95% exact binomial CI.

9.4.3. Efficacy Analyses: Phase 1 and Phase 2

Table 12: Efficacy Endpoints Definition and Statistical Analysis Method (Phase 1 and Phase 2)

Definitions and Statistical Analysis Method	Phase 1	Phase 2
The proportion of subjects with CR or PR (ORR) at Cycle 7 Day 1 (Day 168) is defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD. Exact 95% confidence intervals will be calculated for the true ORR.	Exploratory	Primary
The BOR is defined by the 2104 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD. The proportion of subjects with BOR and 95% CI will be calculated	-	Secondary
Organ-specific response rate (CR or PR) will be assessed based on the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD	Exploratory	Secondary
Failure free survival (FFS) will be defined as the time from first dose of study intervention to unequivocal progression of cGVHD or relapse of underlying malignancy or addition of another systemic immune suppressive therapy or discontinuation of study treatment due to toxicity or death for any reason. FFS will be summarized descriptively using the Kaplan-Meier method	Exploratory	Secondary
The DOR is defined as the time of initial response until documented progression or start of another systemic treatment. DOR will be summarized descriptively using the Kaplan-Meier method	Exploratory	Secondary
The SSR of CR/PR ≥20 weeks is defined as rate of CR/PR lasting for at least 20 weeks from the time of initial response. The proportion of subjects with SRR and 95% confidence intervals will be calculated.	Exploratory	Secondary
Changes in subject-reported symptom activity will be assessed using the Lee cGVHD Symptom Scale.	Exploratory	-
Changes in subject-reported symptom activity will be assessed using the Lee cGVHD Symptom Scale. The proportion of subjects with a ≥ 7-point improvement in normalized score and 95% CI will be calculated.	-	Secondary
Joints and fascia response based on refined NIH response algorithm for cGVHD (Inamoto, et al 2020)	-	Secondary

9.4.4. Other Analyses: Phase 1 and Phase 2

Pharmacokinetic and other correlative studies will be summarized and displayed graphically. Trends in levels will be evaluated from before to Cycle 7 Day 1 (Day 168) after starting study intervention. Additional details for PK, PD, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

Other Endpoints and Statistical Analyses	Phase 1	Phase 2
Percent reduction in average daily dose (or equivalent) or discontinuation of corticosteroid use after study entry Percent reduction in average daily dose (or equivalent) or discontinuation of calcineurin inhibitor use, after study entry	Exploratory	Secondary

9.5. Interim Analyses

No formal interim analysis is planned in either Phase 1 or Phase 2.

Following determination of the OBD and RP2D(s), the SRC will conduct a formal review of PK, PD, safety and tolerability assessments.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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 (e.g., 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 subjects.
- 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 subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects 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.

- The medical record must include a statement that written informed consent was obtained before the subject 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.
- Subjects 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 subject or the subject's legally authorized representative.

A subject 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 subject the objectives of the future research. Subjects 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 subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate in this optional research will not provide this separate signature.

10.1.3. Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject 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 Subject.
- The subject 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. Safety Review Committee (SRC)

The SRC, consisting of investigators and Sponsor, will review safety parameters of each cohort as specified in the SRC charter. In Phase 1, the SRC will be convened after each dose cohort to determine whether the dose should be expanded, escalated or de-escalated. In addition, the SRC will recommend the OBD and RP2D(s) for further evaluation as specified in the SRC charter. The SRC will continue to meet on an ad hoc basis to evaluate emerging safety data from Phase 2.

The SRC may recommend stopping the study if at any time during the study there are unacceptable AEs or safety concerns as described in the protocol stopping rules defined in the SRC charter.

For each SRC meeting, pre-specified reports will be provided by the data management group. In addition, the SRC Chair will be provided with or have access to periodical safety and efficacy reports as specified in the SRC charter. The SRC Chair may share these reports with the SRC or convene additional meetings of the SRC at his/her discretion. The SRC Chair may request additional safety and efficacy data based on the review of study data.

Further details regarding data safety monitoring guidelines will be included in the SRC Charter, which is the governing document that supersedes this section of the protocol.

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 subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., 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 (e.g., 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 (e.g., 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 subjects 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 subject 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 subject'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 subjects 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 subjects are detailed in Section 5 of the protocol.
- Laboratory assessments will be done as specified in SoA (Section 1.2). 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)	Red blood cell (RBC)
Hemoglobin	Hematocrit
Platelet count	Coagulation factors, including PT or INR and aPTT (Screening only)
Clinical Chemistries[a]	
Alanine Aminotransferase (ALT)	Aspartate Aminotransferase (AST)
Alkaline phosphatase	Gamma-glutamyl transferase (GGT)
Total bilirubin (fractionated)	Albumin
Calcium	Blood urea nitrogen (BUN)
Sodium	Creatinine
Chloride	Potassium
Glucose	Bicarbonate
Phosphorus/phosphates	Lactic dehydrogenase
Uric acid	Total protein
Amylase	Magnesium (Screening only, unless clinically indicated)
Lipase	Creatine Kinase

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 End of Treatment visits).
Other Laboratory Assessments	
SNDX-6352 ADA (to be evaluated by central laboratory)	
Bone turnover markers (to be evaluated by central laboratory): • Bone alkaline phosphatase (BAP) • C-terminal telopeptide (CTX)	
Coagulation studies, including PT or INR and aPTT	
Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential[b]	
HCV RNA[c]	

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 6.5 (DLT) and Section 6.7 (dose modification).
[b] For female subjects 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 2 cycles (8 weeks)
[c] Polymerase chain reaction is required and must be negative for HCV RNA in subjects 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 subject or clinical investigation subject 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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Worsening of a pre-existing medical condition, (i.e., 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 NOT 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 subject'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 subject's condition. • Medical or surgical procedure (e.g., 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 (e.g., 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 (i.e., places the subject at immediate risk of death) The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 subject 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 (e.g., 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 subject 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:
• DLTs • Infusion-related reactions including hypersensitivity reactions • irAEs • 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 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 (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the CRF/SAE form. • It is not acceptable for the Investigator to send photocopies of the subject'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 subject identifiers, with the exception of the subject 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 (e.g., 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 subject 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 subject's removal from treatment or from the study. A subject may also voluntarily withdraw consent from treatment due to what she/he perceives as an intolerable AE. If either of these situations arises, the subject 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 subject 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.

Assessment of Causality

Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., 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 (e.g., 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 (e.g., 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 subject's clinical state, environmental or toxic factors, or other therapy administered to the subject
- 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 subjects, 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 subject 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 AESI should be immediately reported (latest within 24 hours of knowledge of the event) to Syndax by completing the SAE report. AESI, 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: [redacted] 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 [redacted] • 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 (i.e., 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 enrollment.

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 (e.g., 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 subject's medical records, medical examination, or medical history interview.

Contraception Guidance:

Female subjects 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 criteria 9 in Section 5.1 for study requirements for female and male subjects.

Subjects with childbearing potential should use highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in Table 14. These contraceptive methods must be used for at least 90 days after the last dose of study intervention. Subjects 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 subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Note that some contraception methods are not considered highly effective (e.g., 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 • Levonorgesterel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g., Implanon® or Norplan® • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g., NuvaRing® • Injection: Medroxyprogesterone injection: e.g., Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g., 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 subjects who become pregnant, and female partners of male subjects

- 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 subject or partner of a male subject 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 subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject 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 subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject 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 – Physician 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 %

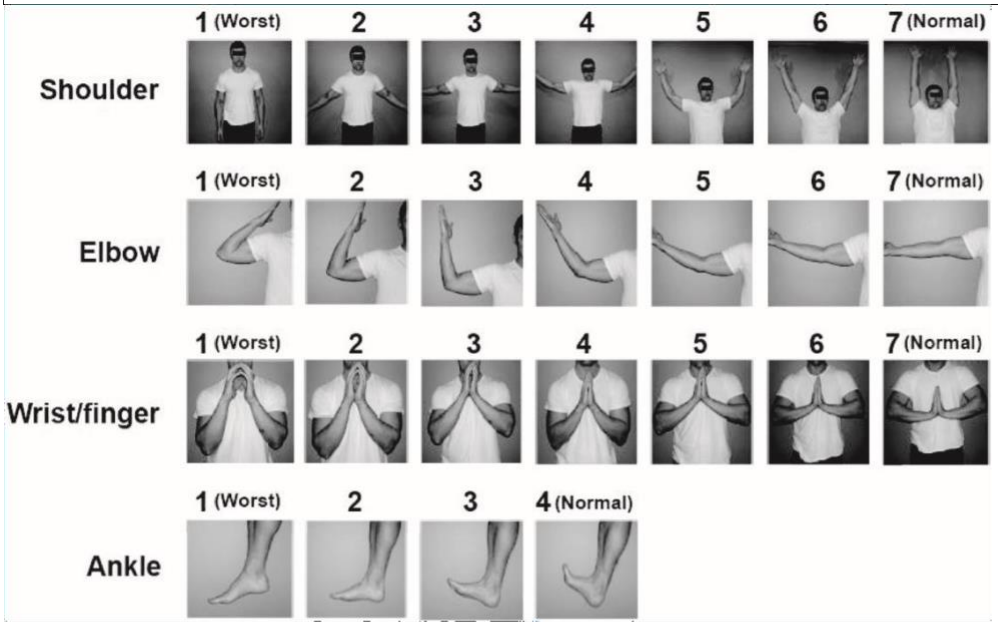
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify 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, et al 2015)

10.5.2. cGVHD Lee Symptom Scale

Please let us know whether you have been bothered by any of the following problems in the past month.

	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
EYES AND MOUTH:					
f. Dry eyes	0	1	2	3	4
g. Need to use eyedrops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING:					
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION:					
q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS:					
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY:					
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL:					
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4

Source: (Lee, et al 2002)

10.6. Appendix 6: Abbreviations

Abbreviation Term	Description
ADL	Activity of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Elevation of Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BAP	Bone Alkaline Phosphatase
BUN	Blood Urea Nitrogen
CCL3	Chemokine (C-C Motif) Ligand 3
cGVHD	Graft Vs. Host Disease
CIOMS	International Organizations of Medical Sciences
CK	Creatine Kinase
CNI	Calcineurin Inhibitor
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CSF-1	Colony Stimulating Factor 1
CSF-1R	Colony Stimulating Factor 1 Receptor
CSR	Clinical Study Report
CTX	C-Terminal Telopeptide
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DREs	Following Disease Related Events
ECP	Extracorporeal photopheresis
EDC	Electronic Data Capture
FAS	Full Analyses Set
FDA	Food and Drug Administration

Abbreviation Term	Description
FFS	Failure Free Survival
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GLDH	Glutamate Dehydrogenase
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HEENT	Head, Ears, Eyes Nose and Throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRT	Hormonal Replacement Therapy
HSCT	Hematopoietic Stem Cell Transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committees
IHC	Evaluated by Immunohistochemistry
IL	Interleukin
INR	International Normalized Ratio
irAEs	Immune-Related Adverse Events
IRB	Institutional Review Boards
ITT	Intent-to-Treat
IV	Intravenous
kg	Kilograms
LFT	Liver Function Test
mAb	Igg4 Monoclonal Antibody
MABEL	Minimum Anticipated Biological Effect Level
MCP1	Monocyte Chemoattractant Protein 1
MTD	Maximum Tolerated Dose
NIH	National Institute of Health
NK	Natural Killer

Abbreviation Term	Description
NOAEL	No Observed Adverse Effect Level
OBD	Optimal Biologic Dose, defined as the lowest safe dose with the highest rate of biologic activity. Biologic activity is determined by 100% reduction of non-classical monocytes at the time of dose interval and plateaued increase of circulating CSF-1 levels that persist for an entire dosing level.
ORR	Objective Response Rate
PD	Pharmacodynamics
PFT	Pulmonary Function Test
PK	Plasma Pharmacokinetics
PR	Partial Response
PRO	Patient-Reported Outcome
RBC	Red Blood Cell
SAE	Serious Adverse Event
SoA	Schedule of Activities
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reactions
TAMs	Tumor-Associated Macrophages
TEAE	Treatment Emergent Adverse Event
TGFb	Transforming Growth Factor B
ULN	Upper Limit of Normal
UVB	Ultraviolet B
WBC	Blood Cell Count
WOCBP	Woman of Childbearing Potential

10.7. Appendix 7: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Prior Amendments

Amendment 9, 27 December 2020

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
6.5 Dose Limiting Toxicity Criteria	≥Grade 3 AST/ALT was removed from the Q4W bullet under non hematologic toxicity DLTsfrom the final bullet in the.	To remove repetition.
6.7.1 Guidelines for Toxicity Management	≥ Grade 3 CK, amylase or lipase in the absence of any clinical symptoms management was adjusted to clarify that if there is end organ damage axatilimab should be discontinued permanently.	To better clarify toxicity management procedures.

Protocol Amendment 8, 12 June 2020

Syndax has introduced the following modifications to protocol V8.0; these changes are presented in order of importance:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3. Objectives and Endpoints 9.4.3 Efficacy analyses	Revised language, reorganized objectives/endpoints, and deleted redundancy. Added secondary objective for Phase 2 dose expansion for joints and fascia response.	For clarity To evaluate effects of SNDX-6352 on joints and fascia
1.1 Synopsis 4.1 Overall Design 6.1 Study Intervention(s) Administered	Updated language to allow evaluation of intermediate dose levels and/or alternative dosing schedules based on emerging data and the evaluation of the safety and tolerability data as a whole.	This language was previously only described in Section 4.2 and 6.1. Language throughout the protocol was updated for consistency.
1.1 Synopsis 4.1 Overall Design 5.1 Inclusion Criterion #3	Modified the following sentence to indicate that the requirement for prior ibrutinib therapy applies to subjects ≥18 years of age: "Subjects ≥18 years of age with active cGVHD who have erythematous rash involving >25% body surface area or a NIH mouth score of >4 must have received prior ibrutinib therapy."	The requirement for prior ibrutinib therapy applies to adult subjects consistent with the approved Prescribing Information for ibrutinib: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/.pdf

Section # and Name	Description of Change	Brief Rationale
1.2 Schedule of Activities (SOA)	Revised the following rows to reflect the dosing schedule for the 3 mg/kg Q4W cohort: • Safety Laboratory: added footnote 9 for Cycle 1 Day 22 indicating samples are not required unless clinically indicated • Clarification of health care provider for cGVHD assessments (footnote 19) • Pharmacokinetics: added a PK sample to be drawn on C1D22 (footnote 23) • Pharmacodynamics (PD): added a PD sample for monocytes to be drawn on C1D22 (footnote 26) The addition of these footnotes resulted in re-numbering of previous footnotes	Adjustments for the 3 mg/kg Q4W cohort due to the monthly dosing schedule
1.2 SoA 5.1 Inclusion Criteria #5 8.1.5 Karnofsky/ Lansky Performance Status scale 5.1 Inclusion Criterion #1, Diagnostic Assessments 9.4.2 Safety Analyses: Phase 1 and Phase 2	Added Lansky performance status scale for patients under 16 years of age	Lansky performance score is routinely used for patients under the age of 16
5.1 Inclusion Criterion #1, Age	Revised Inclusion Criterion #1 to allow subjects 6 years of age or older at the time of signing the informed consent to enter the study. The previous inclusion criterion allowed subjects 12 years of age or older at the time of signing the informed consent to enter the study.	Expand treatment to younger population Lowered the age for eligibility to enter the study to 6 years or older. Investigators have requested this change based on their experience with SNDX-6352 and advice has been sought from the FDA. This change is supported by the safety and pharmacokinetic profile of SNDX-6352 in this study, in patients with advanced cancer, and healthy volunteers.
5.2 Exclusion Criterion #8, Prior/ Concomitant Therapy	Added the following to Exclusion Criterion #8: "For approved or commonly used agents, a washout of 2 weeks or 5 half-lives, whichever is shorter, is required at study enrollment."	For clarity

Section # and Name	Description of Change	Brief Rationale
6.4 Study Intervention Compliance	Clarified observation period for potential infusion.	For clarity
6.5 Dose Limiting Toxicity Criteria, Non-hematologic toxicities	Added the following statement: • "For Q4W dosing only, any asymptomatic ≥Grade 3 AST, ALT, lipase, or amylase that lasts for ≥4 weeks."	Safety measure
6.5 Dose Limiting Toxicity Criteria	Removed the last sentence (shown below) because specific instructions for holding doses of SNDX-6352 are provided in Section 6.7, Dose Modification: "If the dose is held due to toxicity for more than 4 consecutive weeks, permanently discontinue study intervention."	To remove redundancy
6.6.1 Prohibited Medications	Clarified that only 1 systemic corticosteroid is allowed.	For clarity
6.7.1.1 AST, ALT, Bilirubin, CK and Amylase and Lipase 2.3 Benefit/ Risk Assessment	Added toxicity management guidelines for amylase and lipase.	Safety measure
6.7.1.5 Immune-related Adverse Events for SNDX-6352	Added the following footnote to Table 7: "*A delay of SNDX-6352 for up to 6 weeks from the day they were scheduled to receive their next dose is acceptable for subjects who are actively receiving steroid treatment for the management of immune-related adverse events."	Extended the length of time a patient could be off SNDX-6352 to allow for administration and tapering of steroids to manage immune-related adverse events
10.3.6 Reporting of SAEs	Corrected the instructions for sending SAE reports. SAE reports are to be sent to Syndax, rather than to PPD. The email address for submitting SAE reports remains the same: [redacted] Added instructions for reporting AESI.	Corrections and clarifications
General	Ensured consistency and accuracy throughout the protocol, including correcting typographical errors, acronym definitions, formatting and style, as well as alignment across documents.	Administrative

Section # and Name	Description of Change	Brief Rationale
Title Page Protocol Amendment Summary of Changes (SOC) Table 10.7 Appendix 7: Protocol Amendment History	Updated to identify the new Protocol Version number (8), Amendment number (8) and date (12 June 2020). Added a row for the Compound Name, axatilimab. Added the SOC for Protocol Amendment 8 and moved the SOC for Amendment 7 to Section 10.7.	Administrative

Amendment 7, 19 December 2019

Syndax has introduced the following modifications to protocol V7.0, these changes are presented in order of importance:

Section # and Name	Description of Change	Brief Rationale
Title Page 1.1 Synopsis 2.1 Study Rationale 2.3 Benefit/Risk Assessment 3.0 Objectives and Endpoints 4.0 Study Design 4.1 Study Design 4.2 Rationale for Study Design 4.3 Justification for Dose 4.4 End of Study Definition 5.0 Study Population 5.1 Inclusion Criteria 5.2 Exclusion Criteria 8.0 Study Assessments and Procedures 8.2 Efficacy Assessments 8.6 Pharmacodynamics and Exploratory endpoints 9.0 Statistical Considerations 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.3 Populations for Analyses 9.4 Statistical Analyses 10.0 Supporting Documentation and Operational Considerations	Updated language to include a Phase 2, Dose Expansion portion to the study. Up to 22 subjects will be enrolled per cohort.	PK, PD, clinical response and safety data from the Phase 1 indicate that 1 mg/kg of SNDX-6352 is biologically active, induces organ specific responses and improves symptoms with no significant adverse events. Given this, the Phase 2 expansion portion of the study will be used to evaluate the preliminary efficacy of SNDX-6352 at 1 mg/kg.

Section # and Name	Description of Change	Brief Rationale
3.0 Objectives and Endpoints	Updated language to include Phase 2 Expansion primary and secondary objectives and endpoints	PK, PD, clinical response and safety data indicate that 1 mg/kg of SNDX-6352 is biologically active, induces organ specific responses and improves symptoms with no significant adverse events. Given this, the Phase 2 expansion portion of the study will be used to evaluate the preliminary efficacy of SNDX-6352 at 1 mg/kg.
4.0 Study Design Number of Subjects	Update language to include up to 22 patients in Phase 2 dose expansion portion of the study.	PK, PD, clinical response and safety data indicate that 1 mg/kg of SNDX-6352 is biologically active, induces organ specific responses and improves symptoms with no significant adverse events. Given this, the Phase 2 expansion portion of the study will be used to evaluate the preliminary efficacy of SNDX-6352 at 1 mg/kg.
3.0 Objectives and Endpoints	Phase 1 Dose Escalation: update language to include evaluation of reduction in calcineurin inhibitor use.	Standard treatment for cGVHD includes both calcineurin inhibitors and corticosteroids
1.2 Schedule of Assessments 4.0 Study Design	Update language to modify windows for response assessments from ±10 days for each response assessment to ±1 day for Cycle 1 and ±3 days for each subsequent cycle.	Shorten window for response assessment
1.2 Schedule of Assessments 8.2 Efficacy Assessments	Updated language to specify that 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.	To reduce inter-operator bias in cGVHD assessments
1.2 Schedule of Assessments 4.0 Study Design	Clarified language to specify that after 6 cycles of biweekly treatment, in subjects without cGVHD progression, the study intervention may be administered either Q2W or Q4W, at the Investigator's discretion in discussion with the Sponsor	Clarification to language

Section # and Name	Description of Change	Brief Rationale
8.2.1 Response Determination according to 2014 NIH Consensus definitions	Updated language to specify dates for physician-assessed responses (C7D1).	Clarification to language
9.3 Populations for Analyses	Added language to define evaluable populations as subjects who have received at least 1 cycle of treatment and have at least one evaluable response.	Added additional population for analyses
Title Page Protocol Amendment Summary of Changes (SOC) 10.7 Protocol Amendment History	Updated to identify the new Protocol Version number (7), Amendment number (7) and date (16 December 2019) Added the SOC for Protocol Amendment 7 and moved the SOC for Amendment 6 to Section 10.7	Administrative

Amendment 6, 29 August 2019

Syndax has introduced the following modifications to protocol V6.0, these changes are presented in order of importance:

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria	Modified inclusion criterion #3 to indicate prior ibrutinib is required only for subjects with active cGVHD who have erythematous rash involving >25% body surface area or a NIH mouth score of >4.	Investigators are reluctant to prescribe ibrutinib to subjects with cGVHD due to the organ system involvement of the patients that participated in the ibrutinib clinical development program. The ibrutinib pivotal trial required that patients have >25% body surface area erythematous rash or an NIH mouth score of >4 (Miklos, 2017). The change in Inclusion criterion #3 matches the requirement in the ibrutinib pivotal study.
Title Page 1.1 Synopsis 2.1 Study Rationale 4.1 Overall Design	Updated language to reflect the change in Inclusion criterion #3. Revised the Title to remove the requirement for prior ibrutinib therapy for all subjects.	Revised wording to reflect the change in Inclusion criterion #3.

Section # and Name	Description of Change	Brief Rationale
Title Page Protocol Amendment Summary of Changes (SOC) 10.7 Protocol Amendment History	Updated to identify the new Protocol Version number (6), Amendment number (6) and date (29 August 2019) Added the SOC for Protocol Amendment 6 and moved the SOC for Amendment 5 to Section 10.7 Corrected the year for Amendment 5 from 18 Dec 2019 to 18 Dec 2018	Administrative

Amendment 5, 23 July 2019

Syndax has introduced the following modifications to protocol V5.0, these changes are presented in order of importance:

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria	Modify inclusion criteria 1 language	Change eligibility age requirement from 18 years to 12 years of age
1.1 Synopsis 4.1 Overall Design	Update language for clarification	Clarify that after 6 months of biweekly treatment, in subjects without cGVHD progression, the study intervention may be administered every 4 weeks until Month 12 at the Investigator's discretion in discussion with the Sponsor.

Amendment 4, 18 December2018

Syndax has introduced the following modifications to protocol V4.0, these changes are presented in order of importance:

Section # and Name	Description of Change	Brief Rationale
Global change impacting 4.1 Overall Design 8.6 Pharmacodynamics and Exploratory endpoints 9.4.1 OBD Analyses 10.6 Appendix 6: Abbreviations	Update in definition of optimal biologic dose and biologic activity	To clarify OBD definition

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria 6.6.1 Prohibited Medications	Modify inclusion criteria 8 regarding allowed/prohibited medication and updated relevant sections	Per the request of the investigators, allowing prior use of a corticosteroid and calcineurin inhibitor for chronic GVHD to align with standard of care landscape.
9.4 Statistical Analyses	• Update tabular summaries to be provided for safety • Update exploratory analysis (reorder and clarify definition)	• To include additional variables analyzed in tabular summaries (data output, TFLs) • To align with exploratory objectives/endpoints
Section 3 Objectives/Endpoints	• Update safety objective/endpoints • Update and reorder exploratory objectives/endpoints	To reflect changes in statistical section
9.3 Populations for Analyses 9.4 Statistical analysis	Add Full analysis set (FAS) and define which analyses will be done on FAS.	To include a subset of enrolled set who received at least 1 dose of SNDX-6352 and have required baseline data for certain analyses
1.2 Schedule of Activities	• Update • Add clarification footnote regarding pulmonary function test predose on Cycle 1 Day 1	To reflect changes in the protocol and follow standard practice
5.1 inclusion criteria	Modify inclusion criteria 3 language	Language clarification
8.2 Efficacy assessment	PRO corrected to exploratory	To align with objective/endpoints and statistical section
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Update reporting period for AESI with study intervention	To clarify when the reporting period for AESI ends
8.3.5 Pregnancy Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	• Specify for whom pregnancy data will be collected • Update reporting period	• To include female partners of male subjects • To align with SAE and AESI reporting periods
Appendix 3 AE Definitions and Reporting	Change in CRO to PPD and update reporting of SAEs per revised processes	Administrative change
Global change	Update glossary Minor editing, clarifications, typos, style	To reflect changes in protocol To ensure consistency and alignment across document

Amendment 3, 11 July 2018

Syndax has introduced the following modifications to protocol V3.0, these changes are presented in order of importance:

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design	Add a dose escalation decision tree figure	To facilitate understanding of dose escalation process/decision tree
Signature Page	Update sponsor signatory details	Due to personnel changes
Global	Minor style and alignment/consistency changes, correction of typos, update hyperlinks	Minors therefore have not been summarized

Amendment 2, 21 June 2018

Syndax has introduced the following modifications to protocol V2 based on feedback received from the US FDA on June 20, 2018, these changes are presented in order of importance:

Section # and Name	Description of Change	Brief Rationale
Global change impacting Title page 1 Protocol Summary 2 Introduction 3. Objectives/Endpoints 4 Study design 6 Study Intervention 8 Study Assessments 9 Statistical consideration	Removal of dose expansion part	Per FDA, the dose expansion part will be submitted as an amendment to this protocol after the OBD is established.
7.3 Stopping Rules	Removed study stopping rules based on toxicity for dose expansion part	There are built-in stopping rules in the 3+3 dose escalation design.
3. Objectives/Endpoints	Reorganize objectives and endpoints; moved efficacy objective/endpoints to be exploratory. Add pharmacodynamic and other exploratory endpoints for dose escalation.	Organization of objectives and endpoints to match the revised study design
1.1 Synopsis 9 Statistical consideration	Statistical hypothesis, sample size and analyses were updated to align with change in study design and objectives/endpoints	Change in study design triggered changes to statistical consideration section

Section # and Name	Description of Change	Brief Rationale
6.5 DLT Criteria	Clarified DLT assessment window to be 28 days from initiation of treatment with SNDX-6352 or administration of third dose (C2D1), whichever is later and updated DLT section: • add ≥ Grade 3 ALT/AST elevation • removed exception for suspected liver cGVHD at baseline (anything less than a three-fold or greater increase in ALT or AST over baseline will not be considered a DLT unless assessed and reviewed between Investigator and Sponsor medical monitor) • Revised "toxicity resulting in." • Added any adverse event requiring treatment discontinuation or delay ≥ 14 days is a DLT (regardless of CTCAE grade	• Per FDA, allowing 3-fold increases in AST/ALT for patients with baseline liver GVHD may result in a level that falls in the middle of Grade 3 elevations (i.e. 9 x ULN). Patients with baseline liver GVHD are already at greater risk for liver toxicity, and higher levels of hepatotoxicity after treatment with study drug should not be tolerated • Added per FDA request as patients who require a delay in therapy of ≥ 2 weeks for any grade toxicity should be considered to have had a dose-limiting toxicity
4.1 Overall study design	Revised dose escalation text	To facilitate understanding of dose escalation process/decision tree
5.2 Exclusion criteria	Modified exclusion criterion 8	To reflect change in study design
8 Study Assessments	Reorganize order of study assessment	To reflect change in study design
10.1.4 Safety Review Committee	Clarify SRC role in the study	To reflect change in study design
Global	Minor style and alignment/consistency changes, correction of typos, update hyperlinks	Minors therefore have not been summarized

Amendment 1, 18 June 2018

Syndax has introduced the following modifications to protocol v2 based on feedback received from the US FDA on June 14, 2018, these changes are presented in order of importance:

Section # and Name	Description of Change	Brief Rationale
Title 1.1 Synopsis 4.1 Overall design 4.2 Rationale for Study Design	Modified study population to only include subjects with active GVHD who have failed at least 2 prior lines of therapy, including ibrutinib.	Per FDA, ibrutinib is approved as standard of care for second line therapy.

Section # and Name	Description of Change	Brief Rationale
5.1 Study Inclusion		
1.1 Synopsis 3.1 Dose Finding Part	Modified primary objective/endpoint to be based on optimal biologic dose (OBD).	Per FDA, OBD is an appropriate objective/endpoint for this study.
1.1 Synopsis 4.1 Overall design 9.5 Interim analysis	Added gating rules before starting the Dose Expansion part, including definition of OBD, recommended dose, and data review by Safety Review Committee (SRC)	Per FDA, precautionary steps were added prior to initiating the Dose Expansion part.
7.3 Stopping Rules	Added study stopping rules based on toxicity	Per FDA, stopping rules based on toxicity were added as safety measures.
1.2 Synopsis 9.1 Statistical hypothesis 9.2 Sample size determination	Statistical hypothesis and sample size in Dose Expansion were updated to align with change in subject population	Change in study population, triggered changes to statistical hypothesis and sample size determination
6.5 DLT Criteria	Updated DLT section to include: • all events meeting criteria (regardless of relationship to SNDX-6352), • revised exception for asymptomatic Grade ≥2 AST to Grade 2 AST • revised exception for suspected liver cGVHD at baseline (anything less than a three-fold or greater increase in ALT or AST over baseline will not be considered a DLT unless assessed and reviewed between Investigator and Sponsor medical monitor) • removed exception for AST/ALT elevations attributed to concurrent drugs • a clarification of exception to Grade 3 electrolyte abnormalities • Grade ≥ 3 periorbital edema and • a clarification that the 6-week time frame for subjects who received <70% of planned dose	• Per FDA, all AEs should be considered relevant to determining dose • Clarified and revised per FDA request • Added per FDA request and previous clinical data; periorbital edema is a known class effect • Aim to have subjects receive 3 doses; 6-week time frame accounts for potential dose administration delays
6.7.1 Guideline for toxicity management	• Removed 'at least possible due to SNDX-6352' for all toxicities, • Removed investigator attribution of at least possibly related to SNDX-6352 • Clarified that for Grade 3 toxicity, subjects who recover will resume study intervention at next lower dose level, • Clarified that prophylaxis measures for infusion related will be standardized	Per FDA request, a conservative approach is adopted with clear instructions to investigators to ensure standardization

Section # and Name	Description of Change	Brief Rationale
4.1 Overall design	Dose escalation rules for first 2 cohorts was updated to reflect 3+3 design if subject experience any Grade 2 AE	Per FDA, toxicity rule was added
2.3 Benefit/Risk assessment	Added concluding remarks	To further justify study conduct.
1.2 SoA 8.2.2 Neurological exam	Added neurological examination at screening, day 1 of each cycle and each follow-up visit and added cautionary statement about operation/driving heavy complex machinery.	Per FDA, added as a safety measure because CSF-1R is expressed in the brain and healthy participants who received SNDX-6352 experienced higher rates of CNS disorders
6.6.1 Prohibited Medication	Revised text to allow only steroids at the time of enrollment; any other immune suppressive agents for treatment of chronic GVHD are not permitted.	Revised to account for change patient population
Global	Minor style and consistency changes, correction of typos	

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SNDX-6352-503 cGVHD Protocol V10_FINAL_12Apr22

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