NCT #NCT04415073

CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of axatilimab for the treatment of hospitalized patients with respiratory signs and symptoms secondary to novel coronavirus disease (COVID-19)
Protocol Number:	SNDX-6352-0505
Study Intervention:	Axatilimab (SNDX-6352)
Study Phase:	Phase 2
Clinical Site:	Up to 10 US sites
Sponsor Name:	Syndax Pharmaceuticals, Inc.
Legal Registered Address:	35 Gatehouse Drive Building D, Floor 3 Waltham, MA 02451
Regulatory Agency Identifier Number(s):	IND: 149316
Version:	3.0, Amendment 2.0
Approval Date:	23 April 2020

SPONSOR SIGNATORY

[redacted] Date

Medical Monitor Name and Contact Information:

[redacted]
Tel: [redacted]
Email: [redacted]

INVESTIGATOR'S AGREEMENT

I have read the attached protocol (SNDX-6352-0505) entitled "A Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of axatilimab for the treatment of hospitalized patients with respiratory signs and symptoms secondary to novel coronavirus disease (COVID-19)," dated 23 April 2020 version 3.0, 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 V3.0, Amendment 2	23 April 2020
Protocol V2.0, Amendment 1	22 April 2020
Original Protocol V1	16 April 2020

Amendment 2, 23 April 2020

Overall Rationale for the Amendment:

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

Section # and Name	**Description of Change**	**Brief Rationale**
Section 9.1 Statistical Rationale and Determination of Sample Size Section 9.2 Operating Characteristics	• Added clarification for the primary analysis by providing a three-category decision guideline. • Revised assumptions concerning the success rate in the control arm from 70% to 76% as consistent with the Agency's feedback. • Added operating characteristics for a three-category decision guideline.	Upon further consideration of the Agency's feedback, Syndax sought advice from [redacted] As a result of his advice, Syndax has clarified the statistical considerations.
Section 9.3 Population for Analyses	• Revised ITT population description to include that the ITT set will be used in the analyses of the primary and secondary endpoints.	For further clarity.
Section 9.4.1 Efficacy Analysis	• Revised language to specify that rather than considering all subjects with missing data on Day 29 as failures, subjects who cannot be documented to be alive or free of respiratory failure on Day 29 will be imputed	Per advice of [redacted].

	using the overall experience from placebo patients who are assessed at Day 29.	
Section 9.5 Interim Analysis	• Revised language to specify that the interim analysis will occur at 50% of information rather than at 40% of information. • Updated an O-Brien-Fleming monitoring boundaries.	Per advice of [redacted] given that this is set up as a screening trial with a modest sample size, the interim analysis will be conducted at 50% of information.
Section 9.5.1 Independent Data Monitoring Committee (IDMC)	• Revised language to highlight that the mission of the IDMC to safeguard the interests of study participants and to enhance trial integrity.	Clarification in language.
General	• Corrected styles, formatting, links and checked spelling • Other minor terminology updates • Update references	For consistency throughout protocol.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of axatilimab for the treatment of hospitalized patients with respiratory signs and symptoms secondary to novel coronavirus disease (COVID-19)

Rationale

Axatilimab (mAb 969.g2; SNDX-6352) is a humanized IgG4 monoclonal antibody (mAb) with high affinity against colony stimulating factor-1 receptor (CSF-1R) under investigation for the prevention or treatment of respiratory signs and symptoms secondary to novel coronavirus disease (COVID-19).

A review of clinical outcomes in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicates the presence of acute respiratory distress syndrome (ARDS) in a significant proportion of patients with severe disease (Wang, 2020; Wu, 2020).

ARDS has been identified as a leading cause of death due to SARS-CoV-2 infection and results from excessive inflammatory cytokines, known as a cytokine storm, generated by the immune response to the virus (Liao, 2020). Immunopathological characteristics of patients with SARS-CoV-2 confirm a significant increase in pro-inflammatory cytokines such as IL-6, with the likely source of these pro-inflammatory cytokines being activated macrophages (Mehta, 2020; Ruan, 2020; Shi, 2020). In addition, a separate study (Zhang, 2020) supports association of elevated numbers of circulating intermediate and pro-inflammatory CD14+CD16+ monocytes in SARS-CoV-2 patients with increased severity, admission into intensive care units (ICU), and longer recovery time. Interleukin (IL)-6, IL-1b, and other cytokines that constitute the cytokine storm are produced by proinflammatory monocyte-derived macrophages, and depletion of these cells has been shown to prevent and reduce the cytokine release syndrome in preclinical disease models (Giavridis, 2018; Norelli, 2018).

Depletion of pro-inflammatory monocyte-derived macrophages may ameliorate the SARS-CoV-2 associated inflammation in the lungs, thereby preserving lung function and reducing the virus-associated mortality. Proliferation and maturation of circulating pro-inflammatory monocyte-derived macrophages is regulated through activation of the CSF-1R by its ligands colony stimulating factor-1 (CSF-1) and IL-34. In addition, signaling through CSF-1R leads to increased tissue-resident macrophage proliferation secondary to inflammation. Two independent approaches to understanding the role of myeloid cell populations in lung inflammation have demonstrated that CSF-1R blockade can reduce the number and function of pro-inflammatory monocytes / macrophages (Anthony, 2014; Joshi, 2020), suggesting that an anti-CSF-1R approach may be particularly active in preventing or reducing SARS-CoV-2 associated inflammation and its consequences.

Axatilimab has been shown to be extremely effective in rapidly depleting circulating pro-inflammatory monocytes in healthy subjects, cancer patients and patients with chronic graft versus host disease (cGVHD) at doses that have been tolerated well. Depleting circulating pro-inflammatory monocytes with axatilimab may provide a broader and more complete dampening of the overactive immune response seen in SARS-CoV-2 patients than

merely targeting individual cytokine signaling pathways, thus providing additional therapeutic benefit. The ability of axatilimab to rapidly deplete circulating pro-inflammatory monocytes in humans is expected to lead to reduction of cytokine storm and subsequent prevention or treatment of respiratory signs and symptoms secondary to COVID-19.

Objectives and Endpoints (Primary and Secondary)

Objectives	Endpoints
Primary	
• To assess important measures of subject benefit (Section 8.1.1)	• Proportion of subjects alive and free of respiratory failure (need for mechanical ventilation, extracorporeal membrane oxygenation (ECMO), non-invasive ventilation >6L oxygen/minute, or clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision-making driven is driven solely by resource limitation) at Day 29
Secondary	
• Secondary clinical improvement outcomes	• Proportion of subjects achieving a ≥ 2 category improvement on 7-point ordinal score relative to the baseline on Day 28 as collected on Day 29 (Section 8.1.2)
	• Time to clinical improvement (TTCI), defined as national early warning score (NEWS) of ≤2 maintained for 24 hours
• To evaluate improvement in oxygenation in hospitalized adults with respiratory signs and symptoms secondary to COVID-19 treated with axatilimab	• Change from baseline to Day 29 or hospital discharge or death, if sooner, in the ratio of peripheral hemoglobin oxygen saturation to fraction of inspired oxygen (SpO_2/FiO_2)
• To evaluate changes in biomarkers following treatment with axatilimab	• Change from baseline to Day 15 or hospital discharge or death, if sooner, in serum concentrations of IL-6, and c-reactive protein (CRP)
• To evaluate the safety and tolerability of axatilimab in the same population	• Frequency and severity of adverse events (AEs) and serious adverse events (SAEs)

Overall Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety and tolerability of axatilimab as an add-on to standard of care (SOC) therapy in hospitalized subjects with respiratory signs and symptoms secondary to COVID-19 compared to SOC treatment.

The study will be comprised of 2 periods: Screening and Treatment. Throughout the study, subjects will be evaluated as specified in the Schedule of Activities (SoA) in Section 1.2.

After signing informed consent form (ICF), potential candidates, who are hospitalized and have documented/confirmed infection with SARS-CoV-2 by RNA polymerase chain reaction (PCR) test performed <72 hours before randomization, will undergo additional screening procedures.

On Day 1, eligible subjects will be randomized in a 1:1 ratio to one of 2 treatment groups, active or control, as shown in Table 3. Screening and randomization may occur on the same day; if so, study assessments conducted at Screening do not need to be repeated on Day 1, unless drug is not administered within 4 hours of randomization. Randomization will be stratified by severity at study entry (Section 6.4). In addition, time from onset of symptoms (fever, cough, etc.) to study entry will be collected and analyzed prospectively. All subjects will receive study intervention intravenously (IV) as an add-on to SOC on Day 1, within 8 hours of randomization and on Day 15. Subjects will be followed for at least 28 days (+3 days) after the first dose of study intervention (Day 29)/end of study (EOS). Subjects who experience an AE should be followed for at least 30 days after last dose or until resolution of the AE.

Subjects will be monitored post-study per standard of care for as long as they continue to shed viral RNA in nasopharyngeal and stool samples.

Number of Subjects and Intervention Groups

Table 1: Treatment Groups

Treatment Group	Dose Level, Schedule and Route of administration f	Number of subjects
Active	Axatilimab 150 mg on Days 1 and 15, IV + SOC	93
Control	Matching placebo + SOC	93

Duration

For each subject, the study is expected to last as follows:

Screening period:	Up to 3 days
Treatment period:	29 days (+3 days)
Post study follow-up	TBD, subjects will be monitored per standard of care for as long as they continue to shed viral RNA in nasopharyngeal and stool samples

Independent Data Monitoring Committee: Yes

1.2. Schedule of Activities

Table 2: Schedule of Activities

General Notes:

- Some visits/study procedures post-discharge can be done via virtual visits or at home visits. Refer to study reference manual for more details.
- Assessments completed as part of standard of care within the protocol defined windows, will not need to be repeated specifically for the protocol.

Study Procedures	**Screening[a]**	**Treatment Period**							**Notes**
		Baseline[a]	**Daily until hospital discharge**				**Daily until hospital discharge**	**EOS**	**a** Screening and Baseline may occur on the same day; if so, study assessments conducted at Screening do not need to be repeated on Day 1, unless drug is not administered within 4 hours of randomization. Early termination (ET); End of Study (EOS)
Day in study	**-3 to -1**	**1**	**2-7**	**8[b]**	**9-14**	**15 [b]**	**16-28[c]**	**29 [b] /ET**	**b** Required out-patient visit if previously discharged
Visit Window (Days)	**NA**	**NA**		**±1**	**±1**	**±1**	**±1**	**+3**	**c** If a subject is discharged from hospital prior to Day 22, an out-patient clinic visit or telehealth visit for follow up should occur on Day 22
Informed consent	X								
Demographics [d]	X								**d.** Includes age, race, and ethnicity.
Eligibility criteria	X								
Documented/confirmed SAR-CoV-2 by RNA PCR	X[e]								**e.** <72 hours before randomization. Polymerase chain reaction (PCR) must be an FDA approved test.
Medical & disease history[f] & prior medications	X								**f.** Including time from onset of symptoms (fever, cough, etc.) to study entry, COVID-19 severity, reason for hospital admission, and any instances if care decisions are made based on resource limitations.
Complete physical examination	X					X			

Study Procedures	Screening[a]	Treatment Period							Notes
		Baseline[a]	Daily until hospital discharge				Daily until hospital discharge	EOS	**a** Screening and Baseline may occur on the same day; if so, study assessments conducted at Screening do not need to be repeated on Day 1, unless drug is not administered within 4 hours of randomization. Early termination (ET); End of Study (EOS)
Day in study	**-3 to -1**	**1**	**2-7**	**8[b]**	**9-14**	**15 [b]**	**16-28[c]**	**29 [b] /ET**	**b** Required out-patient visit if previously discharged
Visit Window (Days)	**NA**	**NA**		**±1**	**±1**	**±1**	**±1**	**+3**	**c** If a subject is discharged from hospital prior to Day 22, an out-patient clinic visit or telehealth visit for follow up should occur on Day 22
Height and weight	X							X[g]	**g,** Weight to be collected at hospital discharge.
Symptoms-directed physical exam		X[h]	X	X	X		X	X	**h.** Not required to be conducted if screening and baseline occur on the same day.
Vital signs[i]	X	X	X	X	X	X	X	X	**i.** Vital signs should also be obtained during or after the infusion, if clinically indicated. Same method for temperature measurement should be used throughout the study.
SpO_2%[j]	X	X	X	X	X	X/	X	X	**j.** Peripheral capillary oxygen saturation (SpO_2) or O_2 by arterial blood gas The lowest ratio for each day should be collected, with the following exceptions. The ratio immediately prior to study entry will be entered. The last ratio before hospital discharge or death (prior to onset of cardiopulmonary arrest) will be entered.
Record FiO_2[k]	X	X	X	X	X	X	X	X	**k.** Fraction of inspired oxygen (FiO_2). If Fi02 not directly obtainable, use method of delivery (e.g. nasal canula, simple mask, rebreather mask) and oxygen flow rate in L/minute.

Study Procedures	Screening[a]	Treatment Period							Notes
		Baseline[a]	Daily until hospital discharge				Daily until hospital discharge	EOS	**a** Screening and Baseline may occur on the same day; if so, study assessments conducted at Screening do not need to be repeated on Day 1, unless drug is not administered within 4 hours of randomization. Early termination (ET); End of Study (EOS)
Day in study	**-3 to -1**	**1**	**2-7**	**8[b]**	**9-14**	**15 [b]**	**16-28[c]**	**29 [b] /ET**	**b** Required out-patient visit if previously discharged
Visit Window (Days)	**NA**	**NA**		**±1**	**±1**	**±1**	**±1**	**+3**	**c** If a subject is discharged from hospital prior to Day 22, an out-patient clinic visit or telehealth visit for follow up should occur on Day 22
Hospital discharge readiness assessment								X[l]	Refer to Section 8.1.4. **l.** To be collected only on day subject is expected to be assessed as discharge ready (anytime during the study) or ET/EOS.
Chest x-ray or CT scan of lungs[m]	X							X[n]	Computed tomography (CT) **m.** Same modality to be used throughout the study, where possible. **n.** as clinically indicated.
Nasopharyngeal swab for or stool analysis SARS-CoV-2 PCR[o]			Days 3, & 5	X	Day 11	X		X	**o.** For any given subject, the same technique for nasopharyngeal swabbing and nostril (if both nostrils are not sampled) should be used throughout the study (Refer to Section 8.1.6).
[redacted]									
NEWS[q]	X	X	X	X	X	X	X	X	**q.** Refer to Section 8.1.3 National early warning score (NEWS)
State of consciousness	X	X	X	X	X	X	X	X	
12-lead electrocardiogram[r]	X							X	**r.** As clinically indicated.

Study Procedures	Screening[a]	Treatment Period							Notes
		Baseline[a]	Daily until hospital discharge				Daily until hospital discharge	EOS	**a** Screening and Baseline may occur on the same day; if so, study assessments conducted at Screening do not need to be repeated on Day 1, unless drug is not administered within 4 hours of randomization. Early termination (ET); End of Study (EOS)
Day in study	**-3 to -1**	**1**	**2-7**	**8[b]**	**9-14**	**15 [b]**	**16-28[c]**	**29 [b] /ET**	**b** Required out-patient visit if previously discharged
Visit Window (Days)	**NA**	**NA**		**±1**	**±1**	**±1**	**±1**	**+3**	**c** If a subject is discharged from hospital prior to Day 22, an out-patient clinic visit or telehealth visit for follow up should occur on Day 22
Safety Laboratory (hematology, & biochemistry)	X	X[s]	X[t]	X	X [t]	X[u]	X [t]	X	**s.** Not required to be repeated if screening and baseline occur on the same day. **t.** Frequency of safety laboratory to be done per standard of care during hospitalization and on Day 3, Day 5 and Day 11. Refer to Appendix 2 (Section 10.2) for full list of clinical laboratory tests. **u.** Safety laboratory values and results to be obtained prior to dosing
Coagulation factors[v]	X								**v.** Frequency per standard of care during hospitalization. Refer to Appendix 2 (Section 10.2)
Serum Pregnancy test (WOCBP only)	X							X	Women of childbearing potential (WOCBP)
Randomization		X							
Study intervention administration		X[w]				X			**w.** On Day 1, study intervention to be administered within 8 hours of randomization.
Adverse events		X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	

Study Procedures	Screening[a]	Treatment Period							Notes
		Baseline[a]	Daily until hospital discharge				Daily until hospital discharge	EOS	**a** Screening and Baseline may occur on the same day; if so, study assessments conducted at Screening do not need to be repeated on Day 1, unless drug is not administered within 4 hours of randomization. Early termination (ET); End of Study (EOS)
Day in study	**-3 to -1**	**1**	**2-7**	**8[b]**	**9-14**	**15 [b]**	**16-28[c]**	**29 [b] /ET**	**b** Required out-patient visit if previously discharged
Visit Window (Days)	**NA**	**NA**		**±1**	**±1**	**±1**	**±1**	**+3**	**c** If a subject is discharged from hospital prior to Day 22, an out-patient clinic visit or telehealth visit for follow up should occur on Day 22
Pharmacokinetics[x, y]		X	Day 3			X			**x.** Sampling time: Day 1: at 30 min (end of infusion) Day 3: if hospitalized, any time Day 15/ET: predose and at 30 min (end of infusion) **y.** PK samples may be used for anti-drug antibody evaluation.
Pharmacodynamics (cytokines)[z]		X	Day 3	X		X		X	Plasma levels of a cytokine panel will be collected predose.
Pharmacodynamics (monocytes)		X							**z.** Plasma levels circulating monocyte number and phenotype (CD14/16) will be collected predose.
Serum CRP and ferritin		X		X		X		X	C-reactive protein (CRP)
IL-6		X		X		X		X	Interleukin-6 (IL-6)
Post-study follow-up								X[aa]	**aa.** Subjects will be monitored per standard of care for as long as they continue to shed viral RNA in nasopharyngeal and stool samples.

2. INTRODUCTION

2.1. Study Rationale and Hypothesis

Axatilimab (mAb 969.g2; SNDX-6352) is a humanized IgG4 monoclonal antibody (mAb) with high affinity against colony stimulating factor-1 receptor (CSF-1R). It was derived from a rat antibody with humanization achieved by grafting complementary determination region sequences, together with key framework region residues, from the parental rat antibody onto appropriate human germline variable region framework sequences. [redacted]

Axatilimab is currently under investigation for the prevention or treatment of respiratory signs and symptoms secondary to novel coronavirus disease (COVID-19).

A review of clinical outcomes in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicates the presence of acute respiratory distress syndrome (ARDS) in a significant proportion of patients with severe disease (Wang, 2020; Wu, 2020).

ARDS has been identified as a leading cause of death due to SARS-CoV-2 infection and results from excessive inflammatory cytokines, known as a cytokine storm, generated by the immune response to the virus (Liao, 2020). Immunopathological characteristics of patients with SARS-CoV-2 confirm a significant increase in pro-inflammatory cytokines such as IL-6, with the likely source of these pro-inflammatory cytokines being activated macrophages (Mehta, 2020; Ruan, 2020; Shi, 2020). In addition, a separate study (Zhang, 2020) supports association of elevated numbers of circulating intermediate and pro-inflammatory CD14+CD16+ monocytes in SARS-CoV-2 patients with increased severity, admission into intensive care units (ICU), and longer recovery time. Interleukin (IL)-6, IL-1b, and other cytokines that constitute the cytokine storm are produced by proinflammatory monocyte-derived macrophages, and depletion of these cells has been shown to prevent and reduce the cytokine release syndrome in preclinical disease models (Giavridis, 2018; Norelli, 2018).

Depletion of pro-inflammatory monocyte-derived macrophages may ameliorate the SARS-CoV-2 associated inflammation in the lungs, thereby preserving lung function and reducing the virus-associated mortality. Proliferation and maturation of circulating pro-inflammatory monocyte-derived macrophages is regulated through activation of the CSF-1R by its ligands colony stimulating factor-1 (CSF-1) and IL-34. In addition, signaling through CSF-1R leads to increased tissue-resident macrophage proliferation secondary to inflammation. Two independent approaches to understanding the role of myeloid cell populations in lung inflammation have demonstrated that CSF-1R blockade can reduce the number and function of pro-inflammatory monocytes / macrophages (Anthony, 2014; Joshi, 2020), suggesting that an anti-CSF-1R approach may be particularly active in preventing or reducing SARS-CoV-2 associated inflammation and its consequences.

Axatilimab has been shown to be extremely effective in rapidly depleting circulating pro-inflammatory monocytes in healthy subjects, cancer patients and patients with chronic graft versus host disease (cGVHD) at doses that have been tolerated well. Depleting circulating pro-inflammatory monocytes with axatilimab may provide a broader and more complete dampening of the overactive immune response seen in SARS-CoV-2 patients than merely targeting individual cytokine signaling pathways, thus providing additional therapeutic benefit. The ability of axatilimab to rapidly deplete circulating pro-inflammatory monocytes in humans is expected to lead to reduction of cytokine storm and subsequent prevention or treatment of respiratory signs and symptoms secondary to COVID-19.

2.2. Background

SARS-CoV-2, a positive-sense single-stranded RNA virus of zoonotic origin, is highly contagious in humans and is the cause of the ongoing worldwide pandemic of COVID-19. As of April 16, 2020, the SARS-CoV-2 has been responsible for more than 2 million infections and 139,000 deaths worldwide (data from https://coronavirus.jhu.edu/).

SARS-CoV-2 is transmitted via respiratory droplets (fomites infectious particles) within a range of about 2 meters and direct contact with contaminated surfaces. The median incubation period was estimated to be 4-5 days, and the majority (97.5%) developed symptoms within 11.5 days (CI, 8.2 to 15.6 days) of infection (Guan, 2020; Lauer, 2020). Higher viral loads are detected soon after symptom onset, with higher viral loads detected in the nose than in the throat (Zou, 2020). The mean viral load of severe cases was around 60 times higher than that of mild cases, suggesting that higher viral loads might be associated with severe clinical outcomes (Liu, 2020).

Initially, SARS-CoV-2 predominantly infects lower airways and binds to angiotensin converting enzyme (ACE)-2 on alveolar epithelial cells (Guo, 2020; Kuba, 2010). It is a potent inducer of inflammatory cytokines. The “cytokine storm” or “cytokine cascade” is the postulated mechanism for organ damage. The virus activates immune cells and induces the secretion of inflammatory cytokines and chemokines into pulmonary vascular endothelial cells (Jiang, 2020).

Clinical symptoms of COVID-19 include fever, cough, and dyspnea (Guan, 2020; Jiang, 2020; Rodriguez-Morales, 2020; Rothan, 2020); a small population of patients also may suffer from gastrointestinal symptoms (Guan, 2020; Guo, 2020). Radiologic features in the lungs include bilateral ground glass opacities on chest x-ray or computed tomography (CT) (Guan, 2020). COVID-19 appears to be more prevalent in males than females (Adhikari, 2020).

There are no approved treatments for COVID-19 or vaccines against SARS-CoV-2. Clinical management is mainly focused on symptomatic and respiratory support. There are few specific antiviral strategies, but several potent candidates of antivirals and repurposed drugs are under urgent investigation (Guo, 2020). Chloroquine phosphate, a drug for treatment of malaria, was shown to have apparent efficacy against COVID-19 associated pneumonia in multicenter clinical studies conducted in China (Gao, 2020). In addition, IL-6 or IL-6-receptor blocking antibodies like tocilizumab (Actemra, Roche-Genentech), sarilumab (Kevzara, Regeneron), and siltuximab (Sylvant, EUSA Pharma) which are FDA-approved for various conditions, including cytokine release syndrome (CRS), are being investigated in critically ill patients with COVID-19-induced hypoxia (Ascierto, 2020; Conti, 2020). Other treatments and therapies include antibiotics,

corticosteroids, mechanical ventilation, oxygen therapy, and continuous renal replacement techniques (CRRT) (Jiang, 2020).

Infection with SARS-CoV-2 leads to a wide range of clinical manifestations ranging from asymptomatic, mild, moderate to severe. The population at greatest risk for severe disease are immune-compromised patients such as the elderly, and subjects with co-morbid diseases (e.g., diabetes, cardiovascular, cancer). The severe cases usually present with pneumonia, which can progress to ARDS and cytokine storm (Adhikari, 2020; Guo, 2020). ARDS is defined by the acute onset of noncardiogenic pulmonary edema, hypoxemia, and the need for mechanical ventilation. Management principles of COVID-19-induced ARDS are mainly supportive and do not differ from the management of ARDS from other causes. Treatment of severe ARDS associated with COVID-19 is an ongoing challenge. Currently, treatment focuses on lung-protective ventilation; no specific pharmacotherapies have been identified (ARDS Definition Task Force, 2012; Goh, 2020; Matthay, 2019; Matthay, 2020). Approximately 14% (95%CI 6.2-21.5%) of hospitalized patients had fatal outcomes (case fatality rate, CFR) (Rodriguez-Morales, 2020). Risk factors associated with the development of ARDS and progression from ARDS to death included older age, neutrophilia, and organ and coagulation dysfunction (Wu, 2020).

2.2.1. Clinical Experience with Axatilimab

The clinical development program for axatilimab includes 3 studies:

- [redacted]
- An ongoing Phase 1 multiple ascending dose study in subjects with solid tumors (SNDX-6352-0502)
- An ongoing Phase 1/2, dose finding and dose expansion study in subjects with cGVHD (SNDX-6352-0503)

A brief description of the pharmacology and safety of axatilimab is provided below.

[redacted]

[redacted]

SNDX-6352-0502 (ongoing)

SNDX-6352-0502, is an open label, multi-center Phase 1 study evaluating the safety, tolerability, PK and PD activity of axatilimab monotherapy (Phase 1a) and axatilimab in combination with durvalumab (Phase 1b) in subjects with unresectable, recurrent, locally-advanced or metastatic solid tumors (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) that are not amenable to standard therapy. [redacted]

[redacted]

SNDX-6352-0503 (ongoing)

SNDX-6352-0503 is a Phase 1 dose finding and Phase 2 dose expansion study evaluating the safety, tolerability, PK/pharmacodynamic (PD), and efficacy of axatilimab in subjects with active cGVHD whose disease has progressed despite at least 2 prior lines of therapy. [redacted]

2.3. Benefit and Risk Analysis

The available nonclinical data and safety clinical data with axatilimab to date support clinical investigation in subjects with respiratory signs and symptoms secondary to COVID-19. Please refer to the axatilimab Investigator's brochure (IB) for known and expected benefits and risks and reasonably expected adverse events of axatilimab.

Expected AEs that may be predicted to occur based on the pharmacologic and toxicology properties of axatilimab, even if not yet observed with axatilimab include periorbital edema, facial swelling, and infusion reactions.

Due to its mechanism of action (pharmacological inhibition of CSF-1R), axatilimab may induce dose-dependent and reversible increases in circulating levels of creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutamate dehydrogenase (GLDH), amylase and lipase (see IB for details). Kupffer cells in the liver (which are involved in the clearance of these enzymes) are in the macrophage lineage and susceptible to axatilimab inhibition of CSF-1R. The expected increases in these enzyme levels are related to decreased clearance from the blood, rather than from drug-induced liver injury and are not associated with

any histopathological changes. Administration of axatilimab has not been associated with clinical manifestations of hepatitis or pancreatitis, or rhabdomyolysis. Furthermore, these laboratory abnormalities were not observed in patients treated at a doses equivalent to those being proposed in the current study. 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 axatilimab is considered acceptable for COVID-19.

Given the underlying scientific basis for testing CSF-1R targeted therapy in respiratory signs and symptoms secondary to COVID-19, the lack of treatment options in COVID-19 population, the conservative dosing strategy and preliminary PK, PD, safety and preliminary evidence of clinical activity seen in prior completed and ongoing studies, the risk of axatilimab in the proposed patient population is justified.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess important measures of subject benefit (Section 8.1.1)	• Proportion of subjects alive and free of respiratory failure (need for mechanical ventilation, extracorporeal membrane oxygenation (ECMO), non-invasive ventilation >6L oxygen/minute, or clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision-making driven is driven solely by resource limitation) at Day 29
Secondary	
• Secondary clinical improvement outcomes	• Proportion of subjects achieving a ≥ 2 category improvement on 7-point ordinal score relative to the baseline on Day 28 as collected on Day 29 (Section 8.1.2)
	• Time to clinical improvement (TTCI), defined as national early warning score (NEWS) of ≤2 maintained for 24 hours
• To evaluate improvement in oxygenation in hospitalized adults with respiratory signs and symptoms secondary to COVID-19 treated with axatilimab	• Change from baseline to Day 29 or hospital discharge or death, if sooner, in the ratio of peripheral hemoglobin oxygen saturation to fraction of inspired oxygen (SpO_2/FiO_2)
• To evaluate changes in biomarkers following treatment with axatilimab	• Change from baseline to Day 15 or hospital discharge or death, if sooner, in serum concentrations of IL-6, and c-reactive protein (CRP)
• To evaluate the safety and tolerability of axatilimab in the same population	• Frequency and severity of AEs and SAEs

Objectives	Endpoints
[redacted]	

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety and tolerability of axatilimab as an add-on to standard of care (SOC) therapy in hospitalized subjects with respiratory signs and symptoms secondary to COVID-19 compared to SOC treatment.

The study will be comprised of 2 periods: Screening and Treatment. Throughout the study, subjects will be evaluated as specified in the Schedule of Activities (SoA) in Section 1.2.

After signing informed consent form (ICF), potential candidates, who are hospitalized and have documented/confirmed infection with SARS-CoV-2 by RNA polymerase chain reaction (PCR) test performed <72 hours before randomization, will undergo additional screening procedures.

On Day 1, eligible subjects will be randomized in a 1:1 ratio to one of 2 treatment groups, active or control, as shown in Table 3. Screening and randomization may occur on the same day; if so, study assessments conducted at Screening do not need to be repeated on Day 1, unless drug is not administered within 4 hours of randomization. Randomization will be stratified by severity at study entry (Section 6.4). In addition, time from onset of symptoms (fever, cough, etc.) to study entry will be collected and analyzed prospectively. All subjects will receive study intervention IV as an add-on to SOC on Day 1, within 8 hours of randomization and on Day 15. Subjects will be followed for at least 28 days (+3 days) after the first dose of study intervention (Day 29)/end of study (EOS)). Subjects who do not receive a Day 15 dose will also be followed for this period of time. Subjects who experience an AE should be followed for at least 30 days after last dose or until resolution of the AE.

Subjects will be monitored post-study per standard of care for as long as they continue to shed viral RNA in nasopharyngeal and stool samples.

Table 3: Treatment Groups

Treatment Group	Dose Level, Schedule and Route of administration f	Number of subjects
Active	Axatilimab 150 mg on Days 1 and 15, IV + SOC	93
Control	Matching placebo + SOC	93

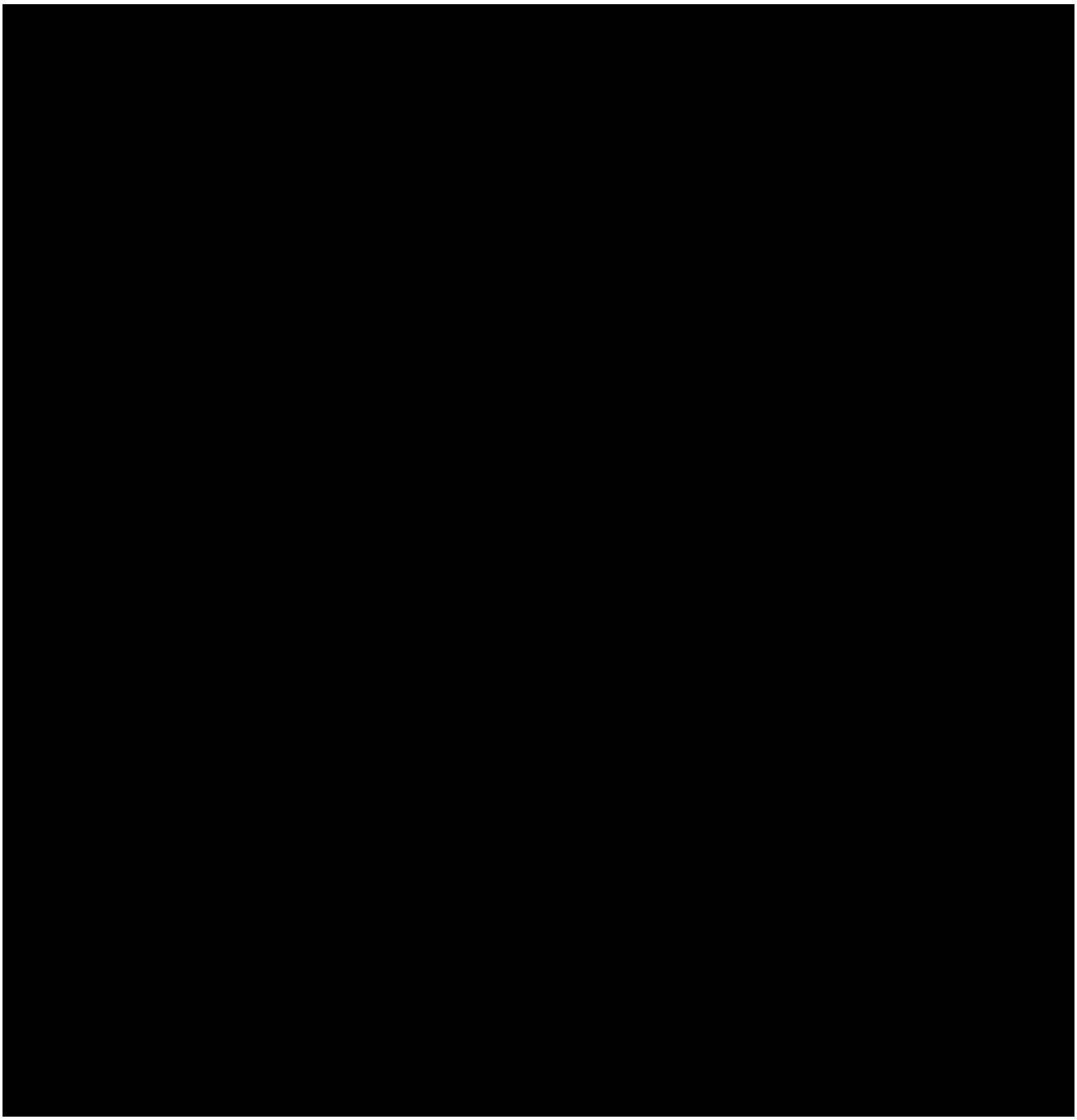
4.2. Scientific Rationale for Study Design

This Phase 2, randomized, double-blind, placebo-controlled study compares 2 treatment groups, active and placebo control. The study intervention will be administered as an add-on therapy to SOC as currently there are no approved treatments for this potentially lethal disease.

4.3. Dose Justification

All subjects will receive axatilimab 150 mg or matching placebo, IV as an add-on to SOC on Day 1, within 8 hours of randomization, and on Day 15.

A flat dose of axatilimab of 150 mg, regardless of body weight, was selected based on nonclinical studies and clinical PK and PD data from healthy volunteers, subjects with solid tumors, and subjects with cGVHD. Although all prior clinical data were obtained with weight-based dosing, review of clinical PK data from those studies showed that a fixed dose (e.g. 150 mg regardless of body weight) gave equally consistent exposure as a weight-based (mg/kg) dose. Therefore, a 150-mg fixed dose will be used both for consistency of exposure (AUC) and to facilitate treatment in this acute care setting, especially if medical resources are strained by surge.



[redacted]

4.4. Study Duration

For each subject, the study is expected to last as follows:

Screening period:	Up to 3 days
Treatment period:	29 days (+3 days)
Post study follow-up	TBD, subjects will be monitored per standard of care for as long as they continue to shed viral RNA in nasopharyngeal and stool samples

4.5. End of Study Definition

A subject is considered to have completed the study if he/she has completed Day 29 visit (or Early termination [ET] visit) or the last scheduled procedure shown in the SoA (Section 1.2).

The end of the study is defined as the date of the last post-study assessment (Day 29 + 3 days) of the last subject in the study.

5. ELIGIBILITY CRITERIA

5.1. Inclusion Criteria

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

Age

1. At least 18 years of age at the time of signing the ICF.

Type of Subject and Disease Characteristics

2. Documented or confirmed SARS-CoV-2 infection by an FDA-approved PCR test of nasopharyngeal swab or stool <72 hours before randomization.
3. Hospitalized for COVID-19.
4. Illness of any duration with at least one of the following
   a. Clinical assessment (evidence of rales/crackles on exam) AND $SpO_2 \leq 94\%$ on room air, or
   b. Requiring mechanical ventilation and/or supplemental oxygen, or
   c. Radiographic evidence (chest x-ray or CT scan) of one of the following:
      – Ground-glass opacities, or
      – Local or bilateral patchy infiltrates, or
      – Interstitial pulmonary infiltrates
5. If the subject is intubated, must have been intubated less than 24 hours prior to randomization.

Sex and Contraception Guidelines

6. Male and/or female subjects.
7. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
8. All subjects (male or female) who are of childbearing potential must agree to use highly effective contraception during the study. Female subjects and male partners of female subjects must continue to use highly effective contraception for 30 days after the last dose of study intervention. Female subjects should not donate oocytes during this time. Male subjects and female partners of male subjects must continue to use highly effective contraception for 90 days. Male subjects must agree not to donate sperm during this time.
9. Women of childbearing potential must have a negative serum pregnancy test at Screening within 72 hours prior to first administration of study intervention.
10. Women not of childbearing potential must be postmenopausal (defined as cessation of regular menstrual periods for at least 1 year.

Informed Consent

11. Capable of giving signed informed consent or by a designated representative as described in Appendix 1 (Section 10.1.2) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Active bacterial pneumonia defined: based on either lobar consolidation on x-ray, positive sputum cultures, or leukocytosis with a left shift.
2. Known active tuberculosis (TB).
3. Subjects with acquired immune deficiency syndrome (AIDS).
4. It is not in the best interest of the subjects to participate, in the opinion of the treating Investigator.
5. In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments.
6. Female subjects who are pregnant or breastfeeding or expecting to conceive within the projected duration of the study, starting with the screening visit through 90 days after the last dose of study intervention.

Diagnostic Assessments

7. The following laboratory parameters are excluded:
   - Hemoglobin <9 g/dL;
   - Absolute neutrophil count $<1.5 \times 10^9$/L;
   - Platelet count $< 50 \times 10^9$/L;
   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 x upper limit of normal (ULN);
   - Total bilirubin >ULN;
   - Serum creatinine >1.5 mg/dL AND creatinine clearance (CrCl) < 45 mL/min/1.73 m^2 based on the Cockcroft-Gault formula.

Excluded Prior/Concomitant Therapy

8. Prior treatment with other agents with actual or possible direct acting anti-inflammatory activity against SARS-CoV-2 in the past 30 days (e.g. chloroquine, hydroxychloroquine).
9. Treatment with convalescent plasma.

10. Treatment with high doses of corticosteroids (>20 mg daily, prednisone equivalent) prior to randomization.
11. Treatment with immunomodulators including anti-IL 6, anti-IL-6 receptor antagonists, or with Janus kinase inhibitors (JAKi) in the past 30 days or plans to receive during the study period.
12. Previous exposure to study intervention or any other agent targeting CSF-1 or CSF-1R or known allergy/sensitivity to study intervention.

Note: subjects on long-term immunosuppressive therapies for pre-existing conditions, such as solid organ transplant, can continue such therapies as long as on stable dose for 1 week prior to study entry.

Note: subjects with cancer who have recently received anti-cancer medications (including immune checkpoint inhibitors) are eligible.

Prior/Concurrent Clinical Study Experience

13. Current participation or have participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.

Note: Subjects participating in an observational study are an exception to this criterion and may qualify for the study with Sponsor approval.

Note: Subjects who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

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 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 4: Study Intervention

Intervention Name	Axatilimab (SNDX-6352)	Placebo
Type	Biologic	Not applicable
Dose Formulation	Solution for infusion	Saline solution for infusion
Unit Dose Strength(s)	50 mg/mL	Not applicable
Dosage Level(s)	Day 1: 150 mg Day 15: 150 mg	Not applicable
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). On Day 1, study intervention to be administered within 8 hours of randomization	
IMP definition	A new drug or biological drug that is used in a clinical investigation (FDA)	Not applicable
Sourcing	Axatilimab is manufactured by [redacted] Study intervention will be provided to the site centrally by the Sponsor or designated representative.	Saline solution for infusion will be provided by the clinical site
Packaging and Labeling	Axatilimab 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 bromobutyl stoppers and sealed with an aluminum overseals and flip-off caps. The vials are single use only and contain no preservatives. Label text for the axatilimab vial will at a minimum include the protocol number, the contents of the vial (e.g., axatilimab 50 mg/mL), lot number, storage conditions, and Sponsor name. Labels comply with regulatory requirements for investigational products.	Not applicable

Former Name(s) or Alias(es)]	UCB-6352	

If the subject has previously been discharged from the hospital, for the Day 15 study intervention dose administration, will be required to attend an out-patient clinic follow-up visit as specified in the SoA (Table 2). The required Day 15 laboratory tests should be obtained prior to Day 15 dosing. Before administering the Day 15 dose, refer to the Dose Modifications Section 6.6. Study intervention will be administered as an IV infusion over 30 minutes; time windows of 5 minutes to +10 minutes are permitted (i.e., infusion time is 25 to 40 minutes). Medical interventions for subjects who have experienced or experience an infusion reaction are addressed in Section 6.6.4.

6.2. Standard of Care

In both study groups, subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator.

Site-specific standard of care will be captured under the concomitant medication electronic case report form (eCRF page).

Refer to Section 6.7 for guidelines on allowed and prohibited medications.

6.3. Preparation/Handling/Storage/Accountability

- 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.
- 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.
- Axatilimab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag and a 50 mL infusion given. No other drugs should be added to the solution for infusion containing axatilimab.
- For a subject receiving a 150 mg dose a total of 4 vials are required. Infusion solution preparation is described in the Pharmacy Manual. The infusion solution can be stored for up to 4 hours at ambient temperature.
- 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).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

All subjects will be centrally assigned to randomized study intervention using an Interactive Response Technology (IRT). Before the study is initiated, the log in information & directions for the IRT will be provided to each site.

Randomization will be stratified by severity of illness at enrollment:

- Critical disease: requiring mechanical ventilation or ECMO
- Severe disease: oxygen requirement of ≥ 4 L/minute, or a $SpO_2 \leq 94\%$ or tachypnoea (respiratory rate ≥ 24 breaths/minute)
- Moderate disease: Oxygen requirement of < 4 L/minute with $SpO_2 \geq 94\%$ and respiratory rate <24 breaths/minute
- Mild disease: $SpO_2 \geq 94\%$ on room air and respiratory rate < 24 breaths/minute without supplemental oxygen.

Study intervention will be dispensed by the unblinded pharmacy staff to the study staff/research nurse in a blinded manner per the schedule summarized in the SoA (Section 1.2).

The IRT will be programmed with blind-breaking instructions. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a subject's study intervention assignment unless this could delay emergency treatment of the subject. If a subject's drug assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

6.5. Study Intervention Compliance

Administration of study intervention 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 electronic case report form (eCRF).

For all study intervention infusions, a mandatory 2-hour observation period for potential infusion-related reactions is required. For subsequent infusion and per the discretion of the investigator, no observation period is required for subjects with no infusion reactions. Subjects who experience an infusion-related reaction at any time, must continue to undergo the mandatory 2-hour observation period after each infusion.

6.6. Dose Modifications

Dose delays for the Day 15 dose but not reductions are allowed in this study.

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 Sponsor's Medical Monitor.

6.6.1. Dose Modifications for AST, ALT, Bilirubin, Creatine Kinase (CK), Amylase and Lipase Elevation

Dose modification guidelines for study intervention due to AST, ALT, bilirubin, CK, amylase or lipase elevation are specified in Table 5.

Table 5: AST, ALT Bilirubin, CK, Amylase and Lipase: Dose Modification Guidelines for Axatilimab for Day 15 dose

Lab abnormality	Dose modifications
Isolated asymptomatic Grade 3 AST or ALT (> 10x ULN but ≤ 20 x ULN) AND total bilirubin Grade ≤1	Hold study intervention until < 10 times ULN; if resolves to < 10 times ULN within 7 days, resume study intervention at the same dose at Investigator's discretion. (only if subject remains hospitalized). if does not resolve within 7 days to < 10 times ULN, permanently discontinue study intervention.
Grade 3 AST or ALT with evidence of end organ damage	Permanently discontinue study intervention.
ALT or AST ≥3 x ULN and simultaneous total bilirubin ≥2 x ULN in the absence of cholestasis or hemolysis	Permanently discontinue study intervention.
Grade 4 AST or ALT (>20 x ULN)	Permanently discontinue study intervention.
Grade 2 total bilirubin	Rule out cholestasis. If ruled out, hold study intervention until recovery to Grade 1, then resume. If evidence of cholestasis, study intervention may be continued without delay after consultation with Sponsor's Medical Monitor.
Grade 3 total bilirubin	Rule out cholestasis. If ruled out, permanently discontinue study intervention. If evidence of cholestasis, study intervention may be resumed after recovery to Grade 1 and consultation with Sponsor's Medical Monitor.
Grade 4 total bilirubin	Permanently discontinue study intervention.
Grade 3 CK, amylase, or lipase in the absence of any clinical symptoms directly attributed to study intervention	Before administering study intervention, conduct diagnostic evaluation, e.g., serum and urine myoglobin, or CK-MB, BUN, creatinine, ECG, troponin (I or T). If results show either no evidence of end organ damage attributable to study intervention OR if end organ damage is attributed to the underlying disease, continue study intervention without delay.

Lab abnormality	Dose modifications
Grade 4 or symptomatic Grade 3 CK, amylase or lipase or Grade 4 CK, amylase, or lipase	Permanently discontinue study intervention.

6.6.2. Dose Modifications for Other Non-hematologic Toxicity

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

Table 6: Other Non-hematologic Toxicity: Dose Modification Guidelines for SNDX-6352 (Day 15)

Toxicity	Dose modifications
Grade 4	Administer symptomatic remedies/start prophylaxis. Any Grade 4 events require permanent treatment discontinuation from study intervention.
Grade 3	Administer symptomatic remedies/ start prophylaxis. Hold study intervention dose until recovery to Grade 1 or baseline under the following directions: 1. If recovered by Day 22, resume study intervention without dose reduction 2. If not recovered by Day 22, permanently discontinue study intervention.
Grade 2	Administer symptomatic remedies / start prophylaxis.

6.6.3. Dose Modifications for Hematologic Toxicity

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

Table 7: Hematologic Toxicity: Dose Modification Guidelines for SNDX-6352 (Day 15)

Toxicity	Dose modifications
Grade 3 to 4 neutropenia, Febrile neutropenia or neutropenic infection; Grade 3 to 4 uncomplicated thrombocytopenia, or	Hold study intervention dose until recovery to Grade 1 or study baseline under the following directions. 1. If recovered by Day 22, resume study intervention without dose reduction.

Toxicity	Dose modifications
Grade 2 complicated thrombocytopenia	2. If not recovered by Day 22, permanently discontinue study intervention.

6.6.4. Axatilimab Infusion-Related Reaction

If a subject experiences a Grade 1 or 2 axatilimab infusion-related reaction, they may continue on study intervention treatment per guidance presented in Table 8. Subjects who previously experienced an infusion-related reaction will receive a premedication regimen of 25 to 50 mg IV or oral equivalent and diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol approximately 30 to 60 minutes prior to each subsequent dose of axatilimab.

Treatment modifications for study intervention infusion-related reactions are outlined in Table 8.

Table 8: Infusion-related Reactions for Study Intervention

NCI-CTCAE Grade	Treatment Modification for study intervention
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease study intervention 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 study intervention 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 study intervention infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study intervention treatment and must not receive any further study intervention.
NSAIDs = nonsteroidal anti-inflammatory drugs	

6.7. Concomitant Medication

All treatments that the Investigator considers necessary for a subject's plan of care may be administered concomitantly with study intervention 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.

Azithromycin is allowed prior and or after study initiation either as an anti-inflammatory agent or as prophylaxis or treatment for bacterial infection.

Anti-viral agents, with the exception of prohibited medications (Section 6.7.1), may be started after the first dose of study intervention and high dose corticosteroids (>20 mg per day, prednisone equivalent) may be initiated in case of clinical deterioration or evidence of adrenal insufficiency while on study intervention.

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

6.7.1. Prohibited Medications

Below is a list of medications that are prohibited **during the study.**

- Chloroquine, hydroxychloroquine
- Convalescent plasma
- Anti-IL 6, anti-IL-6 receptor antagonists, or JAKi
- Systemic anti-cancer treatment including immune checkpoint inhibitors such as cytotoxic T-lymphocyte antigen 4 (CTLA4), anti-programmed cell death 1 (PD-1), and programmed death-ligand 1 (PD-L1) agents
- Agents targeting CSF-1 or CSF-1R
- Investigational agents, other than axatilimab and anti-viral agents

6.8. Treatment of Overdose

For this study, any dose of study intervention greater than the prescribed dose will be considered an overdose. There is no specific treatment recommended to treat an overdose of study intervention and the subject should receive treatment directed towards any symptoms manifested.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor as soon as possible
- Closely monitor the subject for any AE/SAE and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdose

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.

6.9. Intervention after the End of the Study

No additional intervention is planned beyond the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Stopping Rules

The study will be paused to enrollment if there is a greater than 20% absolute difference in serious adverse reactions (SARs) between the two arms at the interim analysis (Section 9.5). Based on unblinded review of data, the independent data monitoring committee (IDMC) may recommend permanent stopping of the study.

There will be close oversight by the Sponsor and IDMC reviews for safety as specified in Section 9.5.1. Additional ad hoc analyses may be convened to ensure patient safety.

7.1.1. Pregnancy

A subject must permanently discontinue study intervention if she is discovered to be pregnant.

7.2. Discontinuation of Study Intervention

In some instances, it may be necessary for a subject to permanently discontinue study intervention. Please also refer to stopping rules described in Section 7.1.

Permanent discontinuation of study intervention does not mean withdrawal from the study, and the subject will be encouraged to remain in the study and continue to complete all study visits. See the SoA (Section 1.2) for data to be collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Subjects may discontinue or be discontinued from study intervention at any time. A subject may discontinue study intervention for reasons including but not limited to:

- Adverse event
- Death
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Lack of efficacy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject* (*only for discontinuing study intervention, but will remain in study)

The reason for subject discontinuation from study intervention will be recorded in the eCRF. At the time of treatment completion or study intervention discontinuation, the Day 15/ET visit

should be completed as shown in the SoA (Section 1.2). Subjects should continue to be followed for safety even if they discontinue study intervention prematurely unless they withdraw consent.

Pregnancy is a mandatory criterion for permanent discontinuation of study intervention (see Section 7.1.1).

7.3. Withdrawal from the Study

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the institution. A subject may withdraw from the study for reasons including but not limited to:

- Death
- Withdrawal by subject
- Lost to follow-up
- Study terminated by Sponsor

The reason for subject withdrawal from the study will be recorded in the eCRF.

At the time of withdrawal from the study, the Day 15/ET visit should be completed, as shown in the SoA (Section 1.2).

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.4. Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to engage 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

- Study procedures and their timing are summarized in the SoA (Section 1.2). Protocol waivers or exemptions are not allowed. Assessments completed as part of standard of care within the protocol defined windows, will not need to be repeated specifically for the protocol.
- 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 screening information including details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Missed visits should be avoided if at all possible; if a visit is missed and cannot be rescheduled, the subject should resume their original visit schedule at the next scheduled visit. Some visits/study procedures can be done via virtual visits or at home visits after hospital discharge. The Day 22 visit may be a remote or an in-clinic visit if subject was discharge from the hospital per SoA (Table 2). Refer to study reference manual for more details.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Table 2).

8.1.1. Measure of Clinical Benefit

At each study day while hospitalized, the following measure of clinical support should be assessed:

- Oxygen requirement (yes / no)
- Non-invasive mechanical ventilation (via CPAP/BiPAP mask) (yes / no)
- Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube) or Extracorporeal membrane oxygenation (ECMO) requirement (yes / no)
- Level of consciousness: alert vs. (arousable only to voice or pain or unresponsive)

In addition, date of hospital discharge readiness or date of hospital discharge (if different) will be collected.

8.1.2. Clinical Status Ordinal Score

Clinical status will be assessed using the 7-point ordinal score (Table 9). The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded (i.e. on Day 3, Day 2 score is obtained and recorded

as Day 2). This scale has been used successfully as an endpoint for evaluation of treatments for severe influenza requiring hospitalization (Peterson, 2017).

Table 9: A 7-Point Ordinal Score for Assessing Clinical Status

Score	Description
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities
3	Hospitalized, not requiring supplemental oxygen
4	Hospitalized, requiring supplemental oxygen
5	Hospitalized, on non-invasive ventilation or high flow oxygen devices
6	Hospitalized, on invasive mechanical ventilation or ECMO
7	Death

8.1.3. National Early Warning Score (NEWS)

The NEWS score has demonstrated an ability to discriminate subjects at risk of poor outcomes. (Smith, 2016; Williams, 2019). This score is based on 7 clinical parameters, vital signs (respiratory rate, temperature, blood pressure, and heart rate), SpO_2, breathing room air or supplemental oxygen, and consciousness (Table 10). The NEWS score is being used as an efficacy measure.

This should be evaluated at the first assessment of a given study day. These parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment. This is recorded for the day obtained.

Table 10: NEW Score

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

Level of consciousness: alert (A), arousable only to voice (V), or pain (P) and unresponsive (U)

8.1.4. Hospital Discharge Readiness Criteria

The subject's readiness for hospital discharge will be evaluated based on the following criteria (must meet all):

- Normal O_2 saturation on room air or a return to pre-morbid status
- Afebrile
- Able to ambulate (or use commode) without assistance or a return to pre-morbid mobility (for non-ambulatory subjects)
- Able to dress self or a return to pre-morbid status
- Eating pre-morbid full diet or a return to pre-morbid status

Date of actual hospital discharge and date of any readmission during the study period should be captured. Subjects' oxygen supplementation status at hospital discharge will also be captured (with vs. without oxygen supplementation).

8.1.5. Oxygenation Measures

Peripheral capillary oxygen saturation (SpO_2) with pulse oximeter may be used as surrogate for arterial blood oxygen saturation or arterial blood gas may be measured. Measurement to be done with the subject laying in prone position, unless indicated otherwise; same position should be used throughout the study; subject position will be captured in the eCRF.

Peripheral hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2) will also be measured.

The lowest ratio for each day should be collected, with the following exceptions. The ratio immediately prior to study entry will be entered. The last ratio before hospital discharge or death (prior to onset of cardiopulmonary arrest) will be entered.

The FiO_2 at the time of the above measurement should also be collected. If the FiO_2 cannot be directly measured via the used oxygen delivery apparatus (e.g., nasal canula, simple mask, rebreather mask), the apparatus used, and flow rate of oxygen in liters/min should be collected.

The ratio of peripheral hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2) will be calculated based on the values obtained above. In case, values are obtained via analysis of arterial blood gases, the following equation will be used for purposes of conversion: $SpO_2/FiO_2 = 64 + 0.84 \times (PaO_2/FiO_2)$.

The lowest ratio for each day should be entered into the eCRF with the following exceptions. The ratio immediately prior to study entry will be entered. The last ratio before hospital discharge or death (prior to onset of cardiopulmonary arrest) will be entered.

Oxygenation will be assessed using the categories in Table 11.

Table 11: A 4-Point Oxygen Ordinal Scale for Severity Categories by SpO_2/FiO_2 Ratio

Score	Severity	SpO_2/FiO_2 (mmHg)
0	None	> 315
1	Mild	> 235 to 315
2	Moderate	> 150 to 235
3	Severe	≤ 150

8.1.6. Viral Clearance

Quantitative viral load will be assessed using nasopharyngeal swab SARS-CoV-2 PCR to monitor disease status during the study. Quantitative assessment of viral RNA load in blood and stool will also be performed as per site specific standard of care.

For any given subject, the same technique for nasopharyngeal swabbing and nostril (if both nostrils are not sampled) should be used throughout the study.

Subjects will be monitored post-study per standard of care as long as they continue to shed viral RNA in nasopharyngeal or stool samples.

For more details refer to the laboratory manual.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 2 in Section 1.2).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the head, ears, eyes, nose and throat (HEENT), dermatological, respiratory,

cardiovascular, gastrointestinal, neurological, and lymphatic, and musculoskeletal systems. Height will also be measured and recorded.

- Symptom-directed physical examination will be conducted as clinically indicated.
- Weight will be measured when complete or symptom-directed physical examinations are performed.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiration rate (breaths per minute), and temperature (°F or C; oral, rectal, forehead, aural), will be measured as per standard practice.
- The same units and mode should be used for a subject across all measurements.
- Vital signs will be measured prior to any blood draw that occurs at the same timepoint

8.2.3. Electrocardiograms

- 12-lead ECG will be obtained while subject is in supine position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT (QTcF), intervals. Subject to be resting for at least 2 minutes prior to ECG.
- An ECG may be repeated anytime, as clinically indicated.

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. For the Day 15 dose, safety laboratory values and results to be obtained prior to dosing even in subjects who were discharged previously.
- 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.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE, adverse events of special interest (AESIs) or SAE can be found in Appendix 3 (Section 10.3).

AE severity will be evaluated by the Investigator in accordance with the NCI CTCAE v5.0.

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, AE of Special Interest and SAE Information

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

Table 12 below summarizes the different observation periods for AEs and SAEs.

Table 12: Adverse Event Observation Periods

Type of Event	Adverse Event/Adverse Events of Special Interest	Serious Adverse Event
Reporting period	From consent until Day 29/EOS visit (+ 3 day). Subjects who experience AE should be followed for at least 30 days after last dose of study intervention or until resolution of AE.	From consent until Day 29/EOS visit (+ 3 day) for all SAEs, and any time after the end of study for SAEs believed to be related to study intervention. Subjects who experience SAE should be followed for at least 30 days after last dose of study intervention or until resolution of SAE.
Reporting Timelines to the Sponsor	Entered into the clinical database on an ongoing basis	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 will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). 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.

8.4. Pharmacokinetics

- Whole blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of axatilimab 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 axatilimab. Samples collected for analyses of axatilimab serum concentration may also be used to evaluate safety, efficacy, ADA, and/or pharmacodynamic aspects related to concerns or questions arising during or after the study.
- Subject confidentiality will be maintained. At visits during which blood samples for the determination of PK, and PD related to axatilimab 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.

8.5. Pharmacodynamics and [redacted] Endpoints

Blood samples will be collected and analyzed for biomarker analysis as specified in the SoA (Section 1.2) including IL-6. Additional plasma/serum sample for future biomarker analyses will also be collected and stored.

The Sponsor or designee will supply complete written instructions for handling, processing, storage, and shipping of biomarker samples in the Laboratory Manual.

Samples may be stored for a maximum of 15 years after the last subject's last visit for the study, at a facility selected by the Sponsor, to enable further analysis of biomarker responses to axatilimab.

8.6. 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 cytokine levels that may include IFN-gamma, IL-1beta, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, TNF-alpha and change from baseline compared to PK, safety endpoints

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

Samples will be tested for axatilimab-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 axatilimab.
- Refer to the Study Laboratory Manual for instructions on sample collection and shipment to the central laboratories.

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

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

9. STATISTICAL CONSIDERATION

9.1. Statistical Rationale and Determination of Sample Size

This is a placebo controlled randomized Phase 2 trial is designed to evaluate the study intervention (axatilimab 150 mg), using screening trial methodology presented in Fleming and Richardson (2004). The primary endpoint is the proportion of subjects alive and free of respiratory failure at Day 29; treatment effect will be assessed using a Chi-square statistic.

A total of 186 subjects will be engaged in a 1:1 randomization. The primary analysis of this Phase 2 trial comparing axatilimab vs placebo is formally based on a three-category decision guideline:

1. If the estimated increase in the proportion of subjects alive and free of respiratory failure at Day 29 is less than 1.282 standard errors, (i.e., corresponding approximately to improving a 76% success rate on placebo to less than 83% on axatilimab), then the utility of this regimen in this indication should be reconsidered.
2. If the estimated increase in the proportion of subjects alive and free of respiratory failure at Day 29 is between 1.282 and 1.96 standard errors, (i.e., corresponding approximately to improving a 76% success rate on placebo to between 83% and 88% on axatilimab), then axatilimab quite plausibly is meaningfully more efficacious than placebo and should be evaluated in a confirmatory Phase 3 clinical trial.
3. If the estimated increase in the proportion of subjects alive and free of respiratory failure at Day 29 is at least 1.96 standard errors (i.e., corresponding approximately to improving a 76% success rate on placebo to at least 88% on axatilimab), then axatilimab would be statistically significantly more effective than the placebo control; consideration would be given to the need for a confirmatory Phase 3 clinical trial.

9.2. Operating Characteristics

The operating characteristics for this three-category decision guideline are:

1. The false-positive error rate of the screening procedure is low. In particular, if the axatilimab 150 mg regimen truly provides no improvement in the proportion of subjects alive and free of respiratory failure at Day 29, then there is only a 10% probability of bringing that regimen forward to a Phase 3 trial, and only a 2.5% probability of reaching the false positive conclusion that that regimen provides a statistically significant improvement in efficacy relative to placebo.

The false-negative error rate is low. If axatilimab 150 mg truly provides a 76% vs 90% increase in proportion of subjects alive and free of respiratory failure at Day 29, then there is only a 10% chance that that regimen would be discarded, and thus a 90% probability that it would be evaluated in a subsequent confirmatory Phase 3 trial, and there is a 72% probability that that regimen would have a statistically significant improvement in efficacy (at one-sided $p<0.025$) relative to placebo.

The first key secondary endpoint will be tested hierarchically if the primary endpoint achieves statistical significance. A sample size of 186 (93 per group) will provide approximately 80% power to detect a 30% vs 50% increase in the proportion of subjects achieving a ≥ 2 category

improvement on 7-point ordinal score relative to the baseline at Day 28, based on Chi-Square test with a (one-sided) 2.5% false positive error rate. Statistical significance at two-sided 0.05 level would be achieved with an estimated increase of 30% vs. 44% in the proportion of responders.

9.3. Population for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-treat Set (ITT)	ITT set consists of all subjects who are randomized in study intervention by following intent to treat principle. The ITT set will be used in the analyses of the primary and secondary endpoints.
Modified Intent to Treat (MITT)	MITT consists of all randomized subjects who receive at least one dose of study intervention and on post baseline assessment of SpO_2/FiO_2 ratio.
Per Protocol Analysis Set	Per Protocol Analysis Set consists of all randomized subjects who receive at least one dose of study intervention without any major protocol violations that would impact the assessment of the primary efficacy endpoint.
Safety Analysis Set	Safety Analysis Set consists of all randomized subjects who received at least one dose of study intervention
PK Analysis Set	All subjects who receive at least one dose of axatilimab and have at least one valid plasma concentration of axatilimab determined.
Pharmacodynamic	Subjects who are exposed to axatilimab and have sufficient samples collected to permit pharmacodynamic analyses.

9.4. Statistical Methods

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

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

and ADaM datasets from which a statistical analysis is performed (including interim reviews) will be archived with the Sponsor

9.4.1. Efficacy Analysis

The primary efficacy endpoint the proportion of subjects alive and free of respiratory failure, defined as need for mechanical ventilation, ECMO, non-invasive ventilation >6L oxygen/minute, or clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision-making driven is driven solely by resource limitation at Day 29 will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline severity (mild, moderate, severe, critical). Site will be included in the model. The ITT analysis set will be used.

For the purposes of the primary efficacy endpoint analysis:

- Subjects who are discharged any time prior to Day 29 who are documented to be alive and free of respiratory failure on Day 29 will be considered as success.
- Subjects who cannot be documented to be alive or free of respiratory failure on Day 29 will be imputed using the overall experience from placebo patients who are assessed at Day 29.

To assess the robustness of the primary efficacy analysis, the following additional analyses will be performed for the primary endpoint.

- A logistic regression model with the proportion of subject alive and free of respiratory failure as the response variable and treatment group, baseline 7-point ordinal scale assessments and stratification factor (baseline severity: mild, moderate, severe, and critical) and site as independent variables will be used using the ITT analysis set
- CMH will be performed with subjects who have baseline measurement and at Day 29 post-baseline assessment using the ITT analysis set (completers)
- CMH will be performed using the per protocol analysis set

Endpoints	Analysis Method
Primary	
• Proportion of subjects alive and free of respiratory failure (need for mechanical ventilation, ECMO, non-invasive ventilation >6L oxygen/minute, or clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision-making driven is driven solely by resource limitation) at Day 29	• Proportion of subjects alive and free of respiratory failure at Day 29 will be analyzed using CMH stratified by baseline disease severity (mild, moderate, severe and critical) and site, including the absolute treatment difference (%) from placebo and 95% CIs.

Endpoints	Analysis Method
Secondary	
• Proportion of subjects achieving a ≥ 2 category improvement on 7-piont ordinal score relative to the baseline on Day 28 as collected on Day 29 (Section 8.1.2)	• Proportion of subjects achieving a ≥ 2 category improvement on 7-piont ordinal score relative to the baseline on Day 29 will be analyzed using CMH stratified by baseline severity (mild, moderate, severe and critical) and site, including the absolute treatment difference (%) from placebo and 95% CIs.
• TTCI, defined as NEWS of ≤2 maintained for 24 hours	• TTCI, defined as NEWS of ≤2 maintained for 24 hours will be analyzed using the Kaplan-Meier method and comparison between treatment groups will be made using log-rank test stratified by baseline severity score (mild-moderate vs severe). Subjects will be censored at Day 15 or sooner, if they discontinue the study prior to observing the event.
• Change from baseline to Day 29 or hospital discharge or death, if sooner, in the ratio of SpO_2/FiO_2	• Change from baseline to Day 29 or hospital discharge or death, if sooner, in the ratio of SpO_2/FiO_2 will be analyzed using an analysis of covariance (ANCOVA) model, with treatment as a fixed effect and site as a covariate.
• Change from baseline to Day 15 or hospital discharge or death, if sooner, in serum concentrations of IL-6 and CRP	• Change from baseline to Days 15 or hospital discharge, if sooner, in serum concentrations of IL-6, ferritin, CRP will be analyzed using an ANCOVA model, with treatment as a fixed effect and site as a covariate.
[redacted]	

Endpoints	Analysis Method
[redacted]	

Endpoints	Analysis Method
[redacted]	

Endpoints	Analysis Method
[redacted]	

9.4.2. Safety and Tolerability Analysis

All safety analyses will be performed on the Safety Analysis Set. Safety will be assessed by clinical review of all relevant parameters including vital signs measurements, AEs, SAEs, physical, ECG results, and laboratory values. Summary tables and listings will be provided for all reported TEAEs, defined as AEs that start on or after the first administration of study treatment. The reported AE term will be assigned a standardized preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse event will be summarized based on the number and percentage of subjects experiencing the event by MedDRA system organ class and preferred term. In the event a subject experiences repeat episodes of the same AE, then the event with the highest severity grade and strongest causal relationship to study treatment will be used for purposes of incidence tabulations.

Tabular summaries will be provided for the following:

- All treatment-emergent adverse events
- Treatment-emergent adverse events by relationship to study intervention treatment and maximum severity grade
- Treatment-emergent adverse events with action of study intervention treatment
- Treatment-emergent adverse events with action of study treatment discontinued
- SAEs
- Changes in chemistry and hematology parameters
- Changes in vital signs, weight and ECGs

9.4.3. Other Analyses

Pharmacokinetic and other correlative studies will be summarized and displayed graphically.

Additional details for PK, PD, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock.

9.5. Interim Analysis

There will be close oversight of safety by the Sponsor and ongoing reviews by the IDMC. If there is a greater than 20% absolute difference in SARs between the two arms at the interim analysis, the IDMC may recommend the study be stopped.

An interim safety/lack of benefit analysis will occur at approximately 50% of total information. For the lack of benefit analysis regarding the primary endpoint, the IDMC will be guided by the Lan-DeMets spending function analog of the O'Brien-Fleming boundary. At the 50% total information, (i.e., with 93 primary endpoints), an O-Brien-Fleming monitoring boundary for lack of benefit that protects a 10% false negative error rate against the alternative hypothesis of 76% vs. 90% would terminate when the data are 1.9 standard errors from that alternative, (i.e., corresponding approximately to a 76% success rate on placebo and less than a 72.5% success rate on axatilimab). Further details will be provided in the SAP.

The unblinded statistical team will prepare the IDMC closed reports for IDMC review and recommendations. An additional document on statistical issues related to monitoring will be provided to the prior to interim analyses.

9.5.1. Independent Data Monitoring Committee (IDMC)

The mission of the IDMC will be to safeguard the interests of study participants and to enhance trial integrity. The IDMC will meet on a frequent basis and will review unblinded efficacy and safety data. The IDMC may recommend stopping the study if at any time during trial conduct if there are unacceptable AEs or safety concerns. The members of the IDMC will be listed in a separate IDMC Charter, the governing document that will supersede this section of the protocol.

10. APPENDICES

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (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. 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.

10.1.5. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or eCRF 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 eCRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- 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 eCRF 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.

10.1.6. 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.

10.1.7. 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 ICH-GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study intervention development

10.1.8. 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 clinical laboratory tests detailed in Table 13 will be performed by a local laboratory, except where specified below, at the timing/frequency detailed in the SoA.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations
- Investigators must document their review of each laboratory safety report.

Table 13: Protocol-Required Laboratory Assessments

Hematology	
White blood cell count (WBC) with absolute differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils) Hemoglobin Platelet count	Red blood cell (RBC) with indices (mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]) Hematocrit
Clinical Chemistries	
Alanine aminotransferase (ALT) Alkaline phosphatase Total and direct bilirubin (fractionated) Albumin Calcium Sodium Glucose Chloride Creatine kinase	Aspartate aminotransferase (AST) Gamma-glutamyl transferase (GGT) Blood urea nitrogen (BUN) Lactate dehydrogenase (LDH) Creatinine Potassium Total protein Bicarbonate Amylase Lipase
Other Laboratory Assessments	
• Coagulation panel: International normalized ratio (INR) • IL-6 • D-dimer • Serum ferritin • Serum C-reactive protein (CRP) • Serum pregnancy test • SARS-COV-2 (COVID-19) test (RT-PCR via nasopharyngeal swab). Quantitative assessment of viral RNA load in blood and stool will also be performed as per site specific standard of care.	

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

Adverse Events of Special Interest for Axatilimab are by the Sponsor defined as:
• Any new infection that occurs on study, regardless of infectious agent (e.g., viral or non-viral). The site of infection and source of culture (BAL, tracheal aspirate, sputum, blood, urine etc.) should be recorded.

10.3.4. Definition of Suspected and Unsuspected 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. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a study intervention
Unexpected Adverse events are defined as:
• AE which is not listed in 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. • It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Medical Monitor/ PPD in lieu of completion of the AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by the Medical Monitor/ PPD. 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 to the Medical Monitor. • 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[1]. 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)

[1] Please refer to the CTCAE v5 published on November 2017 at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

AE and SAE Recording

- 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 is obligated to assess the relationship between study intervention (investigational drug and/or study procedures) each occurrence of each AE/SAE according to the categories below.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality in terms of whether the AE/SAE may be related to study intervention and/or study procedures.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Causality Categories:

- **Related**: An event is considered related if there is a reasonable possibility of causal association between the study intervention and the event. This means there is evidence to

Assessment of Causality
suggest a causal relationship between the study intervention and the AE. The AE follows a reasonable temporal sequence from the time of study intervention administration and follows a known response to the study intervention and cannot be reasonably explained by other factors such as the subject's clinical state or other therapeutic interventions, or concomitant drugs administered to the subject. • **Not related**: The available evidence support that the event is related to other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.

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/PPD 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/PPD 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

SAE and AESI Reporting to PPD via email or facsimile
• On discovery, all SAEs and AESIs, regardless of seriousness, should be immediately reported (latest within 24 hours of knowledge of the event) to PPD by completing the SAE report form and email the documents to: [redacted] Please note that this email address is for the reporting of SAE and pregnancy information only. Back-up reporting method: • Back-up reporting method to PPD 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:

A. Premenarchal
B. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate 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 in Section 5.1 for study contraception 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® • Minipillc: 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: Glossary

Abbreviation Term	Description
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody
ADaM	Analysis Dataset Model
AE	Adverse events
AESI	Adverse events of interest
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
cGVHD	Chronic graft versus host disease
CFR (clinic)	Case fatality rate
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CMH	Cochran-Mantel-Haenszel
CrCl	Creatinine clearance
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Corona virus disease 2019
CR	Complete response
CRP	C-reactive protein
CRRT	Continuous renal replacement techniques
CRS	Cytokine release syndrome
CSF-1	Colony stimulating factor-1
CSF-1R	Colony stimulating factor-1 receptor
CT	Computed tomography
CTLA4	Cytotoxic T-lymphocyte antigen 4
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation

Abbreviation Term	Description
eCRF	Electronic case report form
EOS	End of Study
ET	Early termination
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
HEENT	Head ears eyes nose and throat
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone replacement therapy
IB	Investigator's brochure
ICF	Informed consent form
ICU	Intensive care units
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IHC	Immunohistochemistry
IL-6	Interleukin 6
INR	International normalized ratio
IRT	Interactive Response Technology
ITT	Intent-to-treat Set
IV	Intravenous
JAKi	Janus kinase inhibitors
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
NSAID	Non-steroidal anti-inflammatory drug
NEWS	National Early Warning Score
NK	Natural killer
PaO_2	Partial pressure of oxygen
PCR	Polymerase chain reaction

Abbreviation Term	Description
PD	Pharmacodynamic
PD-1	Programmed cell death 1
PD-L1	Programmed death-ligand 1
PK	Pharmacokinetic
PR	Partial response
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RT-PCR	Reverse-Transcriptase Polymerase Chain Reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDTM	Study Data Tabulation Model
SoA	Schedule of Activities
SNP	Single nucleotide polymorphism
SOC	Standard of care
SpO_2	Peripheral capillary oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction
TB	Known active tuberculosis
TEAE	Treatment-emergent adverse event
TTCI	Time to clinical improvement
ULN	upper limit of normal
WBC	White blood cell count
WOCBP	Women of childbearing potential

10.6. Protocol Amendment History

Prior Amendments

Syndax has introduced the following modifications to Protocol Version 3.0. These changes are presented in sequential order:

Amendment 1, 22 April 2020

Overall Rationale for the Amendment:

Syndax has introduced the following modifications to protocol V1.0, these changes are presented in order of appearance:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Study Design 8.3.1 Time Period and Frequency of Collecting AE, AESI and SAE	• Clarified collection periods for AEs for subjects who experience an AE	• Per FDA request
1.2 Schedule of Activities 6.1 Study Intervention(s) Administered 8.2.4 Clinical Safety Laboratory Assessments	• Clarified that dosing to be done as out-patient for subjects who were discharged prior to Day 15 • Clarified procedures for Day 15 dosing in hospitalized and non-hospitalized subjects	• Per FDA request
1.2 Schedule of Activities	• Reorganized SoA notes to use letters (vs. symbols) • Clarified footnotes relating to assessments to be done as out-patient for subjects who are discharged prior to Day 15 • Clarified that safety laboratory results are to be obtained prior to dosing	• For clarity purposes • Per FDA request
Section 6.6. Dose Modifications	• Added dose modifications for non-hematologic and hematologic toxicities • Removed the exception for dose interruption for increased bilirubin due to hemolysis independent of the underlying cause of hemolysis in Table 5	• Per FDA request
Section 6.7 Concomitant Medication	• Clarified use of azithromycin	• Per FDA request

Section # and Name	Description of Change	Brief Rationale
Section 7.1 Stopping Rules	• Specified that the study will be paused to enrollment if there is a greater than 20% absolute difference in SARs between the two arms at the interim analysis	• Per FDA request
Section 8.1.4 Hospital Discharge Readiness Criteria	• Clarified normal oxygen criteria and added that oxygen supplementation status will be captured	• Per input from Investigator
Appendix 2	• Add laboratory parameters mentioned in the SoA (e.g., CK, amylase and lipase)	• For consistency throughout protocol
General	• Corrected styles, formatting and check spelling • Other minor terminology updates • Update glossary	• For consistency throughout protocol

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