aTyr Pharma, Inc.

A Randomized Double-blind Placebo-controlled Study to Evaluate the Safety and Efficacy of ATYR1923 In Adult Patients With Severe Pneumonia Related To SARS-CoV-2 Infection (COVID-19)

Protocol Number: ATYR1923-C-003

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

Study Sponsor:	aTyr Pharma, Inc. 3545 John Hopkins Court Suite #250 San Diego, CA 92121, USA
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SPONSOR SIGNATORY

[redacted]

13 November 2020

Date

aTyr Pharma, Inc.

INVESTIGATOR STATEMENT

I understand that all documentation provided to me by aTyr Pharma, Inc. (aTyr), or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of aTyr and the IRB, except where necessary to eliminate an immediate hazard to a patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

_____ _____

Investigator Signature Date

_____

Printed Name

CLINICAL STUDY SYNOPSIS

Title	A Randomized Double-blind Placebo-controlled Study to Evaluate the Safety and Efficacy of ATYR1923 In Adult Patients With Severe Pneumonia Related To SARS-CoV-2 Infection (COVID-19)
Sponsor	aTyr Pharma, Inc.
Clinical Phase	2
Indication	Treatment of severe pneumonia due to SARS-CoV-2 infection.
Objectives and Endpoints	The objective of this study is to evaluate the safety and preliminary efficacy of ATYR1923, compared to placebo, in subjects with SARS-CoV2-related severe pneumonia not requiring mechanical ventilation.

Primary

- To assess the safety of a single intravenous (IV) dose of ATYR1923. Safety will be assessed by:
  - Incidence of treatment-emergent adverse events (TEAEs), including serious and severe TEAEs, overall and by severity.

Secondary

- To assess the preliminary effects of ATYR1923 on clinical outcome measures of SARS-CoV-2 infection, including:
  - Time to hospital discharge.
  - Time to recovery (World Health Organization [WHO] Ordinal Scale score ≤3).
  - Proportion of patients achieving recovery by Day 14 and Day 28.
  - Duration of supplemental oxygen (O_2) requirement.
  - Number of days with fever (temperature >100.4ºF [38.0ºC]).
  - Change from baseline in WHO Ordinal Scale score on Days 5, 7, 14, 28, and 60.
  - Time to improvement from inpatient hospital admission based on at least a 1 point reduction in WHO Ordinal Scale score.
  - All-cause mortality at Days 14, 28, and 60.

Exploratory:

- To explore the preliminary efficacy of ATYR1923 for SARS-CoV-2 infection by evaluating effects on the following:
  - Change from baseline in supplemental oxygen requirement at Days 3, 5, 10, 14 and discharge.
  - Proportion of patients requiring intubation, and among those patients, number of days of intubation.
- To assess the pharmacodynamics (PD) of a single IV dose of ATYR1923 by measuring inflammatory biomarkers and cytokines including: C-reactive protein (CRP), interferon gamma (INF-γ), interleukin (IL)-6, IL-2, IL-7, IL-10, tumor necrosis factor-alpha (TNFα), macrophage inflammatory protein-1 (MIP1), C-X-C motif chemokine 10 (CXC-10), and monocyte chemoattractant protein-1 (MCP-1).
- To assess the impact of a single IV dose of ATYR1923 by measuring potential markers of COVID-19 disease, including serum ferritin and D-dimer.

Study Design

This is a randomized, double-blind, placebo-controlled study to evaluate the safety, PD, and efficacy of ATYR1923 in hospitalized patients with SARS-CoV-2-related severe pneumonia not requiring mechanical ventilation. SARS-CoV-2 infection will be confirmed using a polymerase chain reaction (PCR) based test during Screening.

Eligible patients will be randomized 1:1:1 to a single IV dose of ATYR1923 1 mg/kg, ATYR1923 3 mg/kg, or placebo. Study drug will be added to standard of care (SOC) per institutional standard for treating SARS-CoV2 infection.

A single dose of study drug will be administered on Day 1. All study drug will be administered in the hospital setting; patients who are intubated after randomization but prior to study drug administration are no longer eligible to receive study drug. As this is a single-dose study, the treatment period is 1 day. Thereafter, all patients will be followed for 60 days post-treatment. The schedule of study assessments over this period is dependent on the duration of hospitalization and whether or not the patient requires intubation (ie, non-intubated and intubated patients).

- ***While hospitalized,*** non-intubated patients will have study assessments performed while hospitalized on Days 2, 3, 4, 5, 6, 7, 10, and Day 14 and/or Discharge.
  - If the non-intubated patient is discharged prior to Day 14, the assessments scheduled for Day 14 and/or Discharge will be completed at the time of discharge. If discharge occurs on another scheduled study assessment day (ie, any day between Day 2 and 10), the Day 14 and/or Discharge assessments

supersede that study assessment day and the patient then will proceed to outpatient telephone contact (TC) follow-up visits.

- If the patient is discharged prior to Day 14, then outpatient TC follow-up visits are to be conducted on Day 7 (as applicable) and Day 14.
- If the non-intubated patient is discharged after Day 14, the patient is to have the assessments scheduled for Day 14 and/or Discharge performed on the day of discharge. If the patient is hospitalized for ≥21 days, the Day 14 assessments are to be performed weekly (Days 21, 28, 35, etc.) until discharge (with the exception of PK, which is to be done only at Day 28). After discharge, the patient will proceed to the next scheduled outpatient TC follow-up visit. (Thus, if a patient remains hospitalized on Day 28, the Day 28 TC follow-up visit need not be conducted.)

- ***In the event a patient is intubated***, SOC assessments and interventions will supersede study assessments while intubated and for the duration of intubation[1], with clinical assessments collected as available per the institution's electronic medical records.
  - Patients will resume the study assessment schedule upon extubation. (Thus, for example, if an intubated patient is extubated on Day 7, they will resume the study assessment schedule on Day 7).
  - Extubated patients will have the assessments scheduled for Day 14 and/or Discharge performed at the time of hospital discharge and will attend Day 28 and 60 TC follow-up visits.
  - If the patient is hospitalized for ≥21 days, assessments (outlined in Section 4.1.1), are to be performed weekly (Days 21, 28, 35, etc.) until discharge (with the exception of PK, which is to be done only at Day 28). After discharge, the patient will proceed to the next scheduled outpatient TC follow-up visit. (Thus, if a patient remains hospitalized on Day 28, the Day 28 TC follow-up visit need not be conducted.)

An independent Data Safety Monitoring Board (DSMB) will review the progress of the study and perform interim reviews of safety data at regular intervals beginning after the 6th patient has been dosed, and at a frequency guided by the enrollment rate and DSMB recommendation.

Number of Subjects Approximately 30 patients.

1 With the exception of the WHO Scale and sample collection for ADA and Jo-1 Ab, which will continue to be collected as per the Schedule of Assessments.

Number *of Study Centers*	Approximately 15 study centers in the United States.
Target Population	Inclusion Criteria 1. Age 18 to 75 years. 2. Confirmation of SARS-CoV2 infection by PCR. 3. Severe pneumonia related to SARS-CoV2 infection, defined as fever or suspected respiratory infection with radiographic abnormalities suggestive of viral pneumonia, plus at least one of the following: – Respiratory rate >30 breaths/min; or – Severe respiratory distress, as determined by the Investigator; or; – Oxygen saturation (SpO_2) ≤93% on room air. 4. Female patients of childbearing potential must be willing to use adequate contraception or refrain from heterosexual intercourse from Screening until 30 days after the last follow-up visit. Male patients, if not infertile or surgically sterilized, must agree to use adequate contraception and not donate sperm or refrain from heterosexual intercourse from Day -1 until 30 days after the last follow-up visit. (Refer to Section 7.1.6.2 for details regarding adequate contraception.) 5. Signed informed consent by patient or designated legal representative. Exclusion Criteria 1. Patient is intubated/mechanically ventilated. 2. In the opinion of the Investigator, patient's progression to death is imminent. 3. Treatment with immunosuppressant/immunotherapy drugs, including but not limited to IL-6 inhibitors, TNF-α inhibitors, anti-IL-1 agents and janus kinase inhibitors within 5 half-lives or 30 days (whichever is longer) prior to Day 1. 4. Use of chronic (>30 days) oral corticosteroids for a non-COVID-19-related condition in a dose higher than prednisone 10 mg or equivalent per day. 5. Weight >165 kg or <40 kg. 6. Class III or IV congestive heart failure as defined by the New York Heart Association (NYHA) or any recent onset of heart failure resulting in NYHA Class III/IV symptoms. 7. Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cardiovascular

	disease within the last 30 days. (Controlled hypertension is not a criterion for exclusion.) 8. Hospitalization for respiratory disease within 1 year before screening, or a history of chronic obstructive or restrictive respiratory disease that limits activity and requires treatment to manage symptoms, including but not limited to, severe asthma, chronic obstructive pulmonary disease (GOLD Stage 2 or higher) bronchiectasis, interstitial lung disease, pulmonary hypertension, or any other respiratory diseases requiring long-term daily oxygen therapy. 9. Renal failure requiring renal replacement therapy. 10. Patient has a chronic infection such as hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV), or known active tuberculosis or history of untreated tuberculosis. 11. History of anti-synthetase syndrome or known Jo-1 positivity prior to Screening. 12. Pregnancy (negative pregnancy test required for women of child-bearing potential). 13. Participation in another clinical study of an investigational agent within 3 months (small molecules), 6 months (biologics) or 5 half-lives of the agent, whichever is longer. 14. Any physical examination findings and/or history of any illness that, in the opinion of the study Investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study.
Length of Study	~ 63 days: • Screening over Days – 7 to -1. • A single-dose of study drug on Day 1. • Post-treatment monitoring during inpatient hospitalization through hospital discharge. • TC follow-up visits after hospital discharge on Days 28 and 60. (If discharged prior to Day 14, TC follow-up visits also will be conducted on Day 7, as applicable, and Day 14.)
Investigational Medical Product(S) Dose/ Route/ Regimen	Single dose of ATYR1923 administered via IV infusion at a dose of 1 mg/kg, 3 mg/kg, or placebo. The study drug dose will be calculated using the patient's weight. No patient will receive an absolute dose >800 mg.
Non-Investigational Medical Product(s)	SOC, per standard institutional practice
Reference Therapy	Placebo (0.9% sterile sodium chloride solution, USP)

Statistical Methods

Sample size

30 subjects randomized 1:1:1 to ATYR1923 1 mg/kg, 3 mg/kg, or placebo, respectively.

Analysis populations

- Modified intent-to-treat population: all subjects randomized who have received any amount of study drug. Subjects will be analyzed as randomized.
- Safety population: all subjects who have received any amount of study drug. Subjects will be analyzed as treated.

Efficacy analyses

Descriptive summary statistics: Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage (n, %) of patients within each classification.

Safety analyses

Safety and tolerability will be assessed through documentation of TEAEs and vital signs and, as available, clinical laboratory and physical examination findings, and any other parameters relevant to safety.

Table 1: Schedule of Assessments

Assessment	Screening	Treatment		Post-Treatment Monitoring During Hospitalization[1]								Out-patient Follow Up[1]
	Day -7 to -1	D1 (pre-dose) baseline	D1 (post-dose)	D2	D3	D4	D5	D6	D7	D10	D14/ Dis-charge[1]	D7, 14, 28, 60 TC[1]
Informed consent	X											
Eligibility check	X											
Radiographic studies	X[2]	X[4]										
Electrocardiograms	X[3]	X[4]										
SARs-CoV-2 Testing[5]	X	X[4]										
Serology (HBsAg, anti-HCV, and anti-HIV 1/2 tests)	X[6]											
Demographics, Medical History, COVID-19 Symptom History[7]	X											
Pregnancy test[8]	X											
Physical examination	X[9]	X[4]										
Vital signs	X	X[10]	X[10]	X[11]								
SpO_2	X[12]	X[13]	X[13]	X[11]								
Temperature	X	X[13]	X[13]	X[11]								
Randomization		X										
Height[14] and weight	X	X[15]										
Study drug administration		X										
WHO Ordinal Scale score[16]		X		X	X	X	X	X	X	X	X	X
Oxygen utilization[17]	X	X	X	X[11]								
Safety laboratory testing (hematology, clinical chemistry), Urinalysis	X[18]	X[18]		X[11]								
Blood sampling (serum) for ATYR1923 PK[19]			X				X		X	X	X	
Blood sampling for Jo-1 Ab and ADA		X					X		X	X	X	
Blood sampling for cytokines/chemokines		X		X	X		X		X		X	
Blood sampling for cardiac troponins, D-dimers, ferritin, NT-proBNP		X		X	X		X		X		X	
Tryptase		X[20]										

Assessment	Screening	Treatment		Post-Treatment Monitoring During Hospitalization[1]								Out-patient Follow Up[1]
	Day -7 to -1	D1 (pre-dose) baseline	D1 (post-dose)	D2	D3	D4	D5	D6	D7	D10	D14/ Dis-charge[1]	D7, 14, 28, 60 TC[1]
Adverse events[21]			X	X	X	X	X	X	X	X	X	X
Concomitant medications	X[22]	X	X	X	X	X	X	X	X	X	X	X
Intensive care unit utilization / Ventilation status[23]			X									

1. This schedule applies for hospitalized, non-intubated patients. Refer to Footnote 2 and Section 4.1.1 for assessments to be performed while intubated.
   If a patient is discharged prior to Day 14, then outpatient TC follow-up visits are to be conducted on Day 7 (as applicable) and Day 14. The assessments to be conducted at the D7 and D14 TC follow-up visits are the same as those indicated for the Day 28 and Day 60 TC follow-up visits.
2. A radiologic study performed within 7 days prior to Day 1 is acceptable to determine study eligibility. If the radiologic study was performed >7 days before Day 1, a repeat radiologic study is to be performed during Screening.
3. ECG is to be collected during Screening if it was performed per SOC.
4. After Screening, findings from any radiographic studies, electrocardiograms, SARs-CoV-2 testing, or abnormal physical examination findings performed per SOC are to be recorded in the eCRF. Furthermore, radiographic images may be collected and submitted to a central reader for review.
5. Confirmation of SARS-CoV-2 infection by PCR is to be performed during Screening. However, if the test was performed at the study center/institution within 7 days before Day 1 and results are available in the medical record, then this test may be used as the confirmatory screening test. If the SARs-CoV-2 test results are older than 7 days or the test was performed at a different location, a repeat test is to be performed.
6. Blood samples for serology may be collected within 7 days before Day 1.
7. COVID-19 symptom history is to include date of onset of symptoms, list of symptoms, radiological test results, and date of initial SARS-CoV-2 positivity.
8. Urine pregnancy test for women of child-bearing potential.
9. If performed at the study center/institution within 7 days before Day 1 and results are available in the medical record, any abnormal physical examination findings are to be documented in the eCRF. Any abnormal physical examination findings from examinations performed per SOC through discharge also are to be recorded in the eCRF. Respiratory findings supportive of severe respiratory distress, if present, are to be documented on the Physical Examination eCRF if not otherwise captured as part of the patients recent COVID-19-related medical history.
10. Day1 vital signs are to be obtained pre-infusion and at 15 and 30 minutes (±5 minutes) and at 1, 2, and 4 hours (±15 minutes) after the start of infusion (SOI). Vital signs will include blood pressure (systolic and diastolic), heart rate, and respiratory rate, recorded after resting for 5 min.
11. After Day 1, temperature, SpO_2, oxygen utilization, vital signs, and safety laboratory tests are to be measured per SOC and recorded in the eCRF.
12. To assess eligibility, one measurement of SpO_2 without supplemental oxygen should be attempted. If not clinically feasible, obtain the measurement with supplemental oxygen. The corresponding level of supplemental O_2 use is to be recorded in the eCRF at screening to confirm eligibility.
13. Day 1 temperature and SpO_2 (by pulse oximetry) readings will be recorded pre-dose then at 1 and 4 hours (±15 minutes) after the SOI.
14. Height may be collected via patient report.
15. Weight is to be measured within 3 days prior to Day 1. If there is a weight change >10% between Day -3 and Day 1, the dose should be recalculated.
16. The WHO Ordinal Scale score is to be determined between 06:00 and 10:00 hours at each designated time point, or per local SOC, and the score closest to 08:00 hours recorded.
17. Supplemental oxygen is to be captured as a concomitant medication.

18. Note that if Screening safety laboratory assessments are performed within 2 days of Day 1, then the pre-dose Day 1 safety laboratory assessments need not be repeated.
19. On Day 1, blood will be drawn for the PK analysis per the following schedule: end of infusion (EOI), and then at any single time point between 4 and 12 hrs after start of infusion (SOI). Samples will then be drawn once daily on Days 5, 7, 10, and 14. A Day 28 sample will be collected from patients who remain hospitalized.
20. To be repeated within 2 hours for any patient experiencing a suspected infusion-related reaction or anaphylaxis.
21. Any new infections are to be documented as AEs. The new infection site and source of culture are to be recorded in the eCRF.
22. Any ongoing medications are to be documented during Screening.
23. In the event that a patient requires intubation, SOC assessments and interventions will supersede study assessments for the duration of intubation; refer to Section 4.1 and Section 4.1.1 for details.

NOTE: Any patient experiencing a suspected infusion-related reaction or anaphylaxis is to be managed as described in Section 9.9.

LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	Antibody
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BNP	B-type natriuretic peptide
COVID-19	SARS-CoV-2 Infection
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
CXC-10	C-X-C motif chemokine 10
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
Gamma-GT	Gamma glutamyl transferase
GCP	Good Clinical Practice
HARS	Histidyl-tRNA synthetase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IFN-γ	Interferon gamma
IgG1	Immunoglobulin G1

Abbreviation	Definition
IL	Interleukin
ILD	Interstitial lung disease
iMod	Human 59 amino acid protein
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
MCP-1	Monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MIP1	Macrophage inflammatory protein-1
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRP2	Neuropilin 2
NYHA	New York Heart Association
O_2	Oxygen
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SOC	Standard of care
SOI	Start of infusion
SOP	Standard operating procedure
SpO_2	Oxygen saturation
SUSAR	Serious unexpected suspected adverse reaction
TC	Telephone contact

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor-alpha
USP	United States Pharmacopeia
WHO	World Health Organization

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1. STUDY PERSONNEL AND ADMINISTRATIVE STRUCTURE

Study Sponsor:

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aTyr Pharma, Inc.

2. INTRODUCTION

2.1. ATYR1923

ATYR1923 is a novel molecular entity that acts as an extracellular immunomodulator and is under development for treatment of interstitial lung disease (ILD). ATYR1923 comprises a human 59 amino acid protein (iMod) fused to the Fc region of human immunoglobulin 1 (IgG1). The amino acid sequence of the 59 amino acid iMod domain in ATYR1923 corresponds identically to the extracellularly active iMod domain of histidyl-tRNA synthetase (HARS) amino acids 2 to 60 (HARS 2-60). In solution, the ATYR1923 molecule forms a homodimer, similar to other Fc fusion proteins.

ATYR1923 may provide a naturally occurring human immunomodulatory function to therapeutically control or balance the human immune system. The mechanism of action of ATYR1923 in T-cells overlaps with the cellular pathology observed in lung sarcoidosis. In nonclinical studies, ATYR1923 has been shown to inhibit cytokines involved in regulation of inflammatory and immune responses and attenuate T-cell activation (Mertsching et al., 2018) As Neuropilin-2 (NRP-2) was recently discovered to bind ATYR1923, and innate immune cells such as dendritic cells and macrophages are known to express NRP-2 (Roy et al., 2017; Schellenburg et al., 2017), further research into the interaction between ATYR1923 and NRP-2 on these cells could potentially elucidate an additional mechanism through which ATYR1923 modulates the immune system.

2.1.1. Clinical Experience with ATYR1923

To-date, ATYR1923 has been evaluated in 1 completed study in normal healthy volunteers (ATYR1923-C-001) and 1 ongoing, blinded placebo-controlled study in patients with active pulmonary sarcoidosis (ATYR1923-C-002); data from this latter study remain blinded.

In Study ATYR1923-C-001, 25 healthy adult subjects were exposed to single doses of ATYR1923 ranging from 0.03 to 5.0 mg/kg. ATYR1923 pharmacokinetics (PK) was dose-proportional over the range of 0.03 mg/kg to 5.0 mg/kg. Terminal elimination phases were parallel, and the mean $t^{1/2}$ was consistent from the 0.1 mg/kg dose onwards, with mean values ranging from 167 to 242 hours, supporting the potential for once-monthly dosing. ATYR1923 was generally well tolerated at all doses tested. No severe treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), or TEAEs leading to study drug modification (dose reduction or discontinuation) were reported. No apparent dose relationship was seen across the range of doses studied with regard to the incidence of TEAEs. Adverse reactions reported were headache, dizziness, and back pain.

The safety profile of ATYR1923 in patients with pulmonary sarcoidosis in Study ATYR1923-C-002 was consistent with that seen in healthy volunteers. No deaths or treatment-related SAEs were reported. Adverse reactions included dizziness, headache, and productive cough (each 2 patients) and back pain, Candida infection (considered related to Symbicort), diarrhea, migraine, rash pruritic, sinus congestion, and urticaria (each 1 patient).

Three (13%) patients experienced a severe (Grade 3) TEAE; no Grade 4 TEAEs were reported. Grade 3 TEAEs included cholecystitis acute, depression, and urticaria, each in 1 (4%) patient.

No ATYR1923-treated subject in Study ATYR1923-C-001 experienced a definitive infusion-related reaction (IRR). However, the occurrence of an IRR could not be ruled out for subject, who experienced mild, transient symptoms of dizziness, abdominal pain, and "feeling cold" followed by back pain. A patient with pulmonary sarcoidosis in Study ATYR1923-C-002 also experienced events considered representative of an IRR, with this patient similarly experiencing mild transient symptoms of dizziness as well as back pain. Other symptoms included a generalized warm sensation and tingling. As data from this study remain blinded, it is unknown whether this patient was exposed to ATYR1923.

To-date, no patient participating in an ATYR1923 clinical study has developed a persistent anti-drug antibody (ADA) response, or has been positive for Jo-1 antibodies (Ab) after ATYR1923 exposure.

2.2. Rationale for ATYR1923 for the Treatment of Severe Pneumonia Related to SARS-CoV-2 Infection (COVID-19)

Emergent data gathered from patients with COVID-19 infection indicate that significant inflammatory infiltration of the lungs and concurrent elevations in pro-inflammatory cytokines/chemokines (ie, cytokine storms) are prominent factors in severe cases that have progressed to acute respiratory distress syndrome (ARDS) (Zhou et al., 2020). Severely ill patients have significant increases in plasma concentrations of several pro-inflammatory cytokines: interleukins (IL)-2, -7, -6 and 10, granulocyte-colony stimulating factor, interferon-monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and tumor necrosis factor-alpha (TNF-α), indicative of a cytokine storm (Wang et al., 2020). Consistent with this acute inflammatory insult, serial computed tomography scans of patients with COVID-19 infection illustrate the rapid development of diffuse interstitial lung injury, which tracks with clinical disease progression (Shi et al., 2020). It has been hypothesized that rapid activation of CD4+T lymphocytes leads to the acute elevations these pro-inflammatory cytokines, resulting in aberrant lung inflammation and leading to potentially fatal lung damage (Zhou et al., 2020).

ATYR1923 decreases the release of inflammatory cytokines, including IL-2, TNF-α, and IL-13 from human T cells activated *in vitro*, substantiating that ATYR1923 directly modulates T-cell responses. Anti-inflammatory and anti-fibrotic effects of ATYR1923 have also been shown in various animal models of immune-mediated acute lung injury. In the bleomycin-induced lung fibrosis mouse and rat models, ATYR1923 significantly reduced inflammation-dependent pulmonary fibrosis and improved respiratory function parameters.

Significant anti-fibrotic activity has also been demonstrated with ATYR1923 treatment in a sclerodermatous chronic graft-vs-host mouse model. In two granuloma-forming, highly inflammatory mouse models of interstitial lung disease, *S. rectivirgula*-induced chronic

hypersensitivity pneumonitis and *P. acnes*-induced sarcoidosis, ATYR1923 treatment led to the reduction of several pro-inflammatory cytokines, including IL-6, MCP-1 and IFN-γ (Burkart et al., 2019). The immunomodulatory activity of ATYR1923 is likely exerted through interaction with the cell-surface receptor NRP-2, which is present on multiple immune cell types and upregulated on alveolar macrophages and inflammatory monocytes in response to inflammatory conditions in the lung. A potential therapeutic effect of ATYR1923 was also investigated in a murine acute lung injury model that reproduces key features of human ARDS. Treatment with ATYR1923 at 3.0 and 10 mg/kg led to a dose-dependent reduction of total neutrophil and alveolar macrophage counts in the lung at 24h post insult.

Thus, a strong scientific rationale exists to investigate ATYR1923 as a treatment for severe respiratory complications related to COVID-19 infection. aTyr is conducting the current study to evaluate ATYR1923 1 mg/kg and 3 mg/kg in adults with severe respiratory complications related to SARS-CoV2 infection. Eligible patients will be adults aged 18 to 75 years, who present with SARS-CoV2-related severe pneumonia not requiring mechanical ventilation. The patient or designated legal representative is required to provide informed consent before the performance of any study-related procedures. The primary objective is determination of the safety of ATYR1923 in this patient population. The effects of ATYR1923 on efficacy outcomes, including oxygen saturation levels, fever and clinical status, is a secondary objective. The effect of ATYR1923 on other outcome measures in this patient population also will be explored.

3. STUDY OBJECTIVES AND ENDPOINTS

The objective of this study is to evaluate the safety and preliminary efficacy of ATYR1923, compared to placebo, in subjects with SARS-CoV2-related severe pneumonia not requiring mechanical ventilation.

3.1. Primary

The primary objective is:

- To assess the safety of a single intravenous (IV) dose of ATYR1923. Safety will be assessed by:
  - Incidence of TEAEs, including serious and severe TEAEs, overall and by severity.

3.2. Secondary

Secondary objective is:

- To assess the preliminary effects of ATYR1923 on clinical outcome measures of SARS-CoV-2 infection, including:
  - Time to hospital discharge.
  - Time to recovery (World Health Organization [WHO] Ordinal Scale score ≤3).
  - Proportion of patients achieving recovery by Day 14 and Day 28.
  - Duration of supplemental oxygen (O_2) requirement.
  - Number of days with fever (temperature >100.4ºF [38.0ºC]).
  - Change from baseline in WHO Ordinal Scale score on Days 5, 7, 14, 28, and 60.
  - Time to improvement from inpatient hospital admission based on at least a 1 point reduction in WHO Ordinal Scale score.
  - All-cause mortality at Days 14, 28, and 60.

3.3. Exploratory

The exploratory objectives are:

- To explore the preliminary efficacy of ATYR1923 for SARS-CoV-2 infection by evaluating effects on the following:
  - Change from baseline in supplemental oxygen requirement at Days 3, 5, 10, 14 and discharge.
  - Proportion of patients requiring intubation, and among those patients, number of days of intubation.
- To assess the pharmacodynamics (PD) of a single IV dose of ATYR1923 by measuring inflammatory biomarkers and cytokines including: C-reactive protein (CRP), interferon

gamma (INF-γ), interleukin (IL)-6, IL-2, IL-7, IL-10, tumor necrosis factor-alpha (TNFα), macrophage inflammatory protein-1 (MIP1), C-X-C motif chemokine 10 (CXC-10), and monocyte chemoattractant protein-1 (MCP-1).

- To assess the impact of a single IV dose of ATYR1923 by measuring potential markers of COVID-19 disease, including serum ferritin and D-dimer.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

Study ATYR1923-C-003 is a randomized, double-blind, placebo-controlled study to evaluate the safety, PD and efficacy of ATYR1923 in subjects with SARS-CoV-2 related severe pneumonia. SARS-CoV-2 infection will be confirmed using a polymerase chain reaction (PCR) based test during Screening. The Investigator, Sponsor, and patient will be blinded to treatment assignment; study center pharmacy personnel will be unblinded.

Eligible patients will be randomized 1:1:1 to a single IV dose of ATYR1923 1 mg/kg, ATYR1923 3 mg/kg, or placebo. Study drug (ATYR1923 or placebo) will be added onto institutional standard of care (SOC) for treating SARS-CoV2 infection.

A single dose of study drug will be administered on Day 1. All study drug will be administered in the hospital setting; patients who are intubated after randomization but prior to study drug administration are no longer eligible to receive study drug. As this is a single-dose study, the treatment period is 1 day. Thereafter, all patients will be followed for 60 days post-treatment. The schedule of study assessments over this period is dependent on the duration of hospitalization and whether or not the patient requires intubation.

- ***While hospitalized***, non-intubated patients will have study assessments performed on Days 2, 3, 4, 5, 6, 7, 10, and Day 14 and/or Discharge.
  - If the non-intubated patient is discharged prior to Day 14, the assessments scheduled for Day 14 and/or Discharge will be completed at the time of discharge. If discharge occurs on another scheduled study assessment day (ie, any day between Day 2 and 10), the Day 14 and/or Discharge assessments supersede that study assessment day and the patient then will proceed to outpatient telephone contact (TC) follow-up visits.
  - If a patient is discharged prior to Day 14, then outpatient TC follow-up visits are to be conducted on Day 7 (as applicable) and Day 14.
  - If the non-intubated patient is discharged on Day 15-20, the patient is to have the assessments scheduled for Day 14 and/or Discharge performed on the day of discharge. If the patient is hospitalized for ≥21 days, the Day 14 assessments are to be performed weekly (Days 21, 28, 35, etc.) until discharge (with the exception of PK, which is to be done only at Day 28). After discharge, the patient will proceed to the next scheduled outpatient TC follow-up visit. (Thus, if a patient remains hospitalized on Day 28, the Day 28 TC follow-up visit need not be conducted.)

- ***In the event a patient is intubated***, SOC assessments and interventions will supersede study assessments for the duration of their intubation[2], with clinical assessments collected as available per the institution's electronic medical records (see Section 4.1.1).
  - Intubated patients will resume the study assessment schedule upon extubation. (Thus, for example, if an intubated patient is extubated, they will resume the study assessment schedule on Day 7).
  - Extubated patients will have the assessments scheduled for Day 14 and/or Discharge performed at the time of hospital discharge and will attend Day 28 and 60 TC follow-up visits.
  - If the patient is hospitalized for ≥21 days, assessments (outlined in Section 4.1.1), are to be performed weekly (Days 21, 28, 35, etc.) until discharge (with the exception of PK, which is to be done only at Day 28). After discharge, the patient will proceed to the next scheduled outpatient TC follow-up visit. (Thus, if a patient remains hospitalized on Day 28, the Day 28 TC follow-up visit need not be conducted.)

An independent Data Safety Monitoring Board (DSMB) will review the progress of the study and perform interim reviews of safety data at regular intervals beginning after the 6th patient has been dosed, and at a frequency guided by the enrollment rate and DSMB recommendation.

4.1.1. Assessments During Intubation

In the event that a patient requires intubation, SOC assessments and interventions will supersede study assessments for the duration of intubation, with the exception of the WHO Scale and sample collection for ADA and Jo-1 Ab, which will continue to be collected as per the Schedule of Assessments (Table 1) on Days 5, 7, 10, 14 and weekly thereafter. The following clinical assessments will be collected and analyzed as available per the institution's electronic medical records.

- Date and time of intubation and extubation.
- Adverse events (AEs) (including new infections). In the case of new infections, the site and source of culture are to be recorded.
- Concomitant medications.

Patients requiring intubation will have the assessments scheduled for Day 14 and/or Discharge performed at the time of hospital discharge and will attend Day 28 and 60 TC follow-up visits.

2 With the exception of the WHO Scale and sample collection for ADA and Jo-1 Ab, which will continue to be collected as per the Schedule of Assessments.

If the patient is hospitalized for ≥21 days, the Day 14 and/or Discharge assessments are to be performed weekly (Days 21, 28, 35, etc.) until discharge (with the exception of PK, which is to be done only at Day 28).

After discharge, the patient will proceed to the next scheduled outpatient TC follow-up visit. (Thus, if a patient remains hospitalized on Day 28, the Day 28 TC follow-up visit need not be conducted.)

4.1.2. Study Completion

The study will be considered complete when the last patient completes the Day 60 TC Follow-up visit and any necessary follow-up for Jo-1 Ab positivity or ongoing study drug-related TEAEs has been completed.

4.2. Discussion of Study Design

Single and repeated doses of ATYR1923 were found to be safe and well tolerated in a in healthy volunteers and patients with pulmonary sarcoidosis. No significant immunogenic responses (induction of ADAs or Jo-1 Ab positivity) were observed following the administration of single or repeated doses of ATYR1923. The PK of a single dose of ATYR1923 was well characterized and demonstrated dose-proportional exposures over the range of doses from 0.03 to 5 mg/kg following IV drug administration. Terminal elimination phases were parallel, and the mean half-life was consistent from the 0.1 mg/kg onwards, with mean values ranging from 167 to 242 hours.

These data support the continued clinical evaluation of ATYR1923, a novel molecular entity that acts as an extracellular immunomodulator and is under development for treatment of ILD. A strong scientific rationale exists to investigate ATYR1923 as a treatment for patients with severe pneumonia related to SARS-CoV-2 infection (COVID-19), a heavily compromised patient population representing a significant unmet medical need.

Several design features have been employed in the current study in an effort to minimize bias, including a double-blind design, with patients randomized to treatment with ATYR1923 1 mg/kg, 3 mg/kg, or placebo. Random assignment of patients avoids bias and helps ensure that both known and unknown risk factors are distributed evenly between treatment groups. The use of placebo control permits prospective comparison between the ATYR1923 groups and the control group.

This study will be conducted at multiple-study centers. This multi-center design is needed not only for efficient enrollment of the required number of patients, allowing for a more efficient evaluation of ATYR1923, but it provides a better basis for the subsequent generalization of study findings (ICH, 1998).

The current study is specifically designed, with the inclusion of detailed safety measures, to evaluate these parameters in patients with severe pneumonia related to SARS-CoV-2 infection (COVID-19).

Patients will be evaluated for 60 days after study drug exposure.

The development of humoral immune responses (formation of Ab) to exogenously administered proteins occurs commonly. ATYR1923 is a protein-based therapeutic; specifically, it is a human 59-amino acid protein (ie, iMod) directly fused to the C-terminus Fc region of human IgG1, and exists as an Fc fusion dimer. The immunogenicity assessments in clinical ATYR1923 studies include assessment of both ADA and Jo-1 Ab, the Ab that recognizes HARS, with loss of immune tolerance to HARS being associated with anti-synthetase syndrome. No significant immunogenic responses (persistent induction of ADAs or Jo-1 Ab positivity) have been observed in patients participating in an ATYR1923 clinical study to date. However, ADA have occurred infrequently in nonclinical studies with ATYR1923 in the rat and non-human primate. ADA did not affect the PK of the drug. Thus, ADAs may be observed in the current clinical study. Accordingly, the study design includes ADA and Jo-1 Ab testing, detailed clinical monitoring for adverse immunological events, extended safety follow-up if indicated to follow-up on serological findings, and a specific plan to assist Investigators in the clinical management of patients in whom immunogenicity occurs (see Section 9.9).

The Investigator will take all the usual medical safety precautions necessary for studies at an early stage in the development of a new drug and has full discretion to stop study drug infusion at any time, if clinically warranted, or otherwise in the patient's best interest (Section 6.4).

5. STUDY POPULATION

Approximately 30 patients with severe pneumonia related to SARS-CoV-2 infection (COVID-19) are planned to be enrolled in this study.

5.1. Inclusion Criteria

The following inclusion criteria must be met for a patient to be eligible for inclusion in the study:

1. Age 18 to 75 years.
2. Confirmation of SARS-CoV2 infection by PCR.
3. Severe pneumonia related to SARS-CoV2 infection, defined as fever or suspected respiratory infection with radiographic abnormalities suggestive of viral pneumonia, plus at least one of the following:
   - Respiratory rate >30 breaths/min; or
   - Severe respiratory distress, as determined by the Investigator; or;
   - Oxygen saturation (SpO_2) ≤93% on room air.
4. Female patients of childbearing potential must be willing to use adequate contraception from Screening until 30 days after the last follow-up visit. Male patients, if not infertile or surgically sterilized, must agree to use adequate contraception and not donate sperm from Day -1 until 30 days after the last follow-up visit. (Refer to Section 7.1.6.2 for details regarding adequate contraception.)
5. Signed informed consent by patient or designated representative.

5.2. Exclusion Criteria

A patient who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Patient is intubated/mechanically ventilated.
2. In the opinion of the Investigator, patient's progression to death is imminent.
3. Treatment with immunosuppressant/immunotherapy drugs, including but not limited to IL-6 inhibitors, TNF-α inhibitors, anti-IL-1 agents and janus kinase inhibitors within 5 half-lives or 30 days (whichever is longer) prior to Day 1.
4. Use of chronic (>30 days) oral corticosteroids for a non-COVID-19-related condition in a dose higher than prednisone 10 mg or equivalent per day.
5. Weight >165 kg or <40 kg.
6. Class III or IV congestive heart failure as defined by the New York Heart Association (NYHA) or any recent onset of heart failure resulting in NYHA Class III/IV symptoms.

7. Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cardiovascular disease within the last 30 days. (Controlled hypertension is not a criterion for exclusion.)
8. Hospitalization for respiratory disease within 1 year before screening, or a history of chronic obstructive or restrictive respiratory disease that limits activity and requires treatment to manage symptoms, including but not limited to, severe asthma, chronic obstructive pulmonary disease (GOLD Stage 2 or higher) bronchiectasis, interstitial lung disease, pulmonary hypertension, or any other respiratory diseases requiring long-term daily oxygen therapy.
9. Renal failure requiring renal replacement therapy.
10. Patient has a chronic infection such as hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV), or known active tuberculosis or history of untreated tuberculosis.
11. History of anti-synthetase syndrome or known Jo-1 positivity prior to Screening.
12. Pregnancy (negative pregnancy test required for women of child-bearing potential).
13. Participation in another clinical study of an investigational agent within 3 months (small molecules), 6 months (biologics) or 5 half-lives of the agent whichever is longer.
14. Any physical examination findings and/or history of any illness that, in the opinion of the study Investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study.

5.3. Source of Patients

This will be a multi-center study. Each study center is required to obtain Institutional Review Board (IRB) and regulatory approval to conduct the study before enrollment of patients may commence. Patients meeting the study entry criteria will be eligible for enrollment.

6. STUDY CONDUCT

6.1. Patient Identification, Enrollment, and Randomization

After obtaining informed consent, patients will be screened according to the inclusion and exclusion criteria. Patients will be randomized to one of the three treatment arms based on their availability. Patients who have met all eligibility criteria will receive a unique Screening number according to the Screening order. Then, prior to dosing, each patient will be allocated a randomization number according to their chronological order of inclusion in the study. This number will correspond to a treatment (ATYR1923 or placebo) as specified on the pre-determined randomization schedule.

The master randomization schedule will be made of randomly permuted blocks of appropriate sizes, as determined by the unblinded study team member producing the schedule. The schedule will be generated electronically.

For patients who are replaced, the replacements should take the same treatment assignment as the original patient to ensure that the treatment groups stay balanced.

The randomization code will be produced within the interactive web response system (IWRS). The study center pharmacist or designated unblinded study team member will be provided access to the randomization code within the IWRS. The laboratory where the PK samples are to be analyzed will also be provided access to distinguish between samples of patients dosed with ATYR1923 versus placebo.

Patients who withdraw for any reason without completing all Screening evaluations successfully, will be considered “screen failures”. Such patients will have a limited number of electronic case report forms (eCRFs) completed.

6.2. Patient Management

All patients or their designated legal representatives must provide informed consent before the performance of any study-related procedure. Patients eligible for the study will be randomized within 24 hours before study drug administration on Day 1 and will receive a single dose of study drug (either ATYR1923 or placebo), according to their treatment assignment on a double-blind basis. Patients will have post-treatment follow-up visit assessments performed for 60 days after completion of dosing.

6.3. Patient Adherence

All patients are required to adhere to the protocol-specified dosing and visit schedules. If a patient misses a scheduled visit, attempts should be made to reschedule the visit within the visit windows specified in Table 1.

6.4. Withdrawal and Replacement of Patients

6.4.1. Study Drug Discontinuation Criteria

Study drug administration must be permanently discontinued for a patient if any of the following events occur:

- A SAE that has a reasonable possibility of a causal relationship with the study drug.
- A severe IRR that includes cardiac and/or respiratory observations (see Section 9.9 for Management of IRRs).
- Patient request to discontinue study drug dosing for any reason.
- Other findings that, at the discretion of the Investigator and/or Sponsor, indicate that study drug administration should be discontinued.

The Investigator has full discretion to stop study drug infusion at any time, if clinically warranted or in the patient's best interest.

All patients who have been dosed with any amount of study drug will continue to be followed for safety. Patients who discontinue study drug dosing at any time during the treatment period should return to the study center for the post treatment follow-up visits and as clinically indicated.

Patients who withdraw their consent will not receive any further study drug, but will be offered all follow-up safety assessments.

If a subject fails to attend scheduled study assessments, the Investigator must determine and document the reasons and the circumstances as completely and accurately as possible.

6.4.2. Replacement of Patients

If a patient is withdrawn from the study for any reason, whether related to the study drug or not, or if a patient voluntarily withdraws before or after receiving the study drug, such patient will be considered an early-termination patient.

Investigator will make every effort to ensure that early-termination patients who have received study drug complete the safety follow up assessments.

Patients who are randomized and do not receive study drug will be replaced at the Sponsor's discretion. The decision regarding the replacement of patients will be documented.

6.4.3. Study Withdrawal Criteria

Patients will be informed that they have the right to discontinue from the study and withdraw consent at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the study for any of the following reasons:

- Patient non-adherence to study drug or protocol requirements.
- Patient unwillingness to continue in the study.
- Any other reason, based upon the medical judgment of the Investigator.

The reason for study withdrawal is to be documented in the patient's source documents and electronic case report form (eCRF).

At the time of discontinuation from the study, patients are to have all the assessments planned for the final follow-up visit performed after the last study drug dose, if feasible.

6.5. Study Completion

A patient is considered to have completed the study if they completed all dosing and all follow-up visits.

6.6. Study Termination

If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then this can happen only after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant study termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to discontinue the Study
- A decision on the part of the Sponsor to suspend or discontinue development of ATYR1923.

6.7. Investigator Compliance

If the study center deviates significantly from the protocol, the center may be discontinued from the study. The Investigator is responsible for ensuring the accuracy and completeness of all research records, the accountability of Study Drug, and the conduct of clinical and laboratory evaluations as outlined in the protocol. The Investigator is responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidance documents.

6.8. Data Safety Monitoring Board

Ongoing review of safety and tolerability data will be performed by the Medical Monitor and aTyr Pharma personnel. (The Investigator, Sponsor, and patient will be blinded to treatment assignment).

An independent DSMB will review the progress of the study and perform interim reviews of safety data at regular intervals beginning after the 6th patient has been dosed, and at a frequency guided by the enrollment rate and DSMB recommendation.

The Food and Drug Administration will be notified if any patient is withdrawn for safety reasons and of any decision to pause enrollment or terminate the study.

7. STUDY DRUG

7.1. Study Drug Dose and Administration

7.1.1. Treatments Administered

Patients will be randomly assigned via computer-generated randomization list to 1 of 3 treatment groups at a 1:1:1 ratio as follows:

- Single dose of ATYR1923 1 mg/kg
- Single dose of ATYR1923 3 mg/kg
- Single dose of placebo.

It is planned that study drug will be administered as an IV infusion.

The patient's weight will be used to calculate the ATYR1923 dose. No patient will receive an absolute dose >800 mg. If there is a weight change >10% between Day -3 and Day 1, the dose should be recalculated.

7.1.2. Identity of Investigational Products

7.1.2.1. ATYR1923

The ATYR1923 Drug Product is a sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free liquid concentrate for IV administration. ATYR1923 Drug Product (3.8 mL fill volume) is supplied in a single-use borosilicate glass vial, stoppered with bromobutyl rubber stopper (with FluroTec coating), and sealed with aluminum Flip-off® seal. The formulation of ATYR1923 Drug Product contains 25 mg/mL ATYR1923, 20 mM L-histidine, 125 mM sodium chloride, 3% sucrose, 10 mM L-methionine, and 0.02% polysorbate 20 at pH 6.9.

ATYR1923 will be administered to patients by IV infusion after appropriate dilution in 0.9% sterile sodium chloride solution, United States Pharmacopeia (USP), as outlined in the study Pharmacy Manual.

7.1.2.2. Placebo

Placebo used in this study will be 0.9% sterile sodium chloride solution, USP.

Placebo will be administered to patients by IV infusion as outlined in the study Pharmacy Manual.

7.1.3. Method of Assigning Patients to Treatment Groups

After obtaining informed consent, patients will be screened according to the inclusion and exclusion criteria. Patients who are determined to be eligible, based on Screening assessments, will be randomized on a 1:1:1 basis in a blinded fashion to 1 of 3 treatment groups (ATYR1923

1 mg/kg, ATYR1923 3 mg/kg, or placebo) via the computer-generated randomization list. Patients who are randomized are considered enrolled in the study.

7.1.3.1. Criteria for Pausing Enrollment

In the event that a serious unexpected suspected adverse reaction (SUSAR) has occurred, the enrollment and initiation of study drug administration to new patients will be paused and the Sponsor will request an unblinded review by the DSMB, who will provide its recommendation to aTyr Pharma. Such recommendation may include, but is not limited to, stopping enrollment, continuing the study as planned, or continuing the study with modifications.

In addition, if unexpected, clinically significant trends or changes in other safety assessments are identified during routine safety reviews the Sponsor may request the DSMB to similarly perform a review and provide recommendations.

7.1.4. Selection of Doses in the Study

To date, 25 healthy adult subjects have been exposed to ATYR1923 at doses ranging from 0.03 to 5.0 mg/kg in a first-in-human clinical study. In addition, 24 patients with pulmonary sarcoidosis have participated in an ongoing multiple-dose study. At the time of this document, enrollment in Cohorts 1 and 2 (ATYR1923 1 and 3 mg/kg) has been complete, with DSMB review of blinded data performed. (As the data remain blinded, the number of patients exposed to ATYR1923 is unknown, but, based on the randomization scheme, is assumed to be approximately 16). Doses of 1 and 3 mg/kg are estimated to be pharmacologically active.

To date, no deaths or study drug-related SAEs have been reported with ATYR1923. No apparent dose relationship was seen across the range of doses studied with regard to the incidence of TEAEs. Adverse reactions reported to date include back pain, Candida infection, diarrhea, dizziness, headache, migraine, productive cough, rash pruritic, sinus congestion, and urticaria.

No ATYR1923-treated subject in Study ATYR1923-C-001 experienced a definitive IRR. However, the occurrence of an IRR could not be ruled out for one subject, who experienced mild, transient symptoms of dizziness, abdominal pain, and “feeling cold” followed by back pain. A patient with pulmonary sarcoidosis in Study ATYR1923-C-002 also experienced events considered representative of an IRR, with this patient similarly experiencing mild transient symptoms of dizziness as well as back pain. Other symptoms included a generalized warm sensation and tingling. As data from this study remain blinded, it is unknown whether this patient was exposed to ATYR1923.

No patient participating in an ATYR1923 clinical study was positive for ADA or Jo-1 Ab after study drug exposure.

Given that doses of 1 and 3 mg/kg have been tolerable in both healthy volunteers and patients with pulmonary sarcoidosis and are predicted to be pharmacologically active, these dose levels were selected for use in the current study.

7.1.5. Blinding

The following controls will be employed to maintain the double-blind status of the study:

- The infusion solution for patients assigned to active drug and placebo will be indistinguishable in appearance.
- The study center pharmacist or designated unblinded study team member will have access to random treatment assignments via IWRS for dispensing purposes; treatment assignments will be accessible only to the pharmacist or designated unblinded study team member and will be maintained in a blinded fashion. The study drug infusion will be labeled by the unblinded pharmacist or designated unblinded study team in a blinded manner.

To manage the patient's condition in case of a medical emergency, the Investigator (or delegate) is allowed to break the code in order to identify whether a patient received ATYR1923 or placebo. If the blind is broken for an individual patient, the name of the person who broke the blind and the date and time of and the reason for breaking the blind must be documented. The Sponsor will be informed in case of unblinding. There are no specific antidotes for ATYR1923. Knowledge of whether the patient received ATYR1923 or placebo, may not necessarily help in the care of an individual patient. The need to break the blind must therefore be carefully considered.

The laboratory where the PK samples are to be analyzed will also be provided access to the randomization code within the IWRS to distinguish between samples of patients dosed with ATYR1923 versus placebo.

7.1.6. Concomitant Medication and Other Restrictions During the Study

7.1.6.1. Prohibited or Restricted Concomitant Medications and Substances

The following treatments and procedures are prohibited prior to and/or during study participation, as indicated below:

- All investigational agents or devices (other than ATYR1923) within 3 months for small molecules and 6 months for biologics, or 5 half-lives (if known) of the agent, whichever is longer, before the first study drug dose and through the duration of study drug treatment.
- Use of chronic (>30 days) oral corticosteroids for a non-COVID-19-related condition in a dose higher than prednisone 10 mg or equivalent per day.
- Use of immunosuppressive medications/immunotherapy including but not limited to sarilumab and tocilizumab.
- Off-label use of commercially-available medications for the treatment of SARS-CoV-2.

All other concomitant medications and procedures (including remdesivir) are allowed.

Concomitant medications, including supplemental oxygen, are to be recorded in the source documents and in the eCRF.

7.1.6.2. Contraception

Female patients of childbearing potential must be non-pregnant and non-lactating, and have a negative urine pregnancy test at Screening.

Male patients who are not surgically sterilized and female patients of childbearing potential are required to use adequate contraception from first entry into the clinical research center until 30 days after the last follow-up visit. Male patients who are not surgically sterilized are required to use condoms. Adequate contraception for females of childbearing potential is defined as using hormonal contraceptives, levonorgestrel implants, injectable progestogen, or an intrauterine device combined with at least 1 of the following forms of barrier contraception: a diaphragm or cervical cap, or a condom.

Total abstinence, in accordance with the lifestyle of the patient, is acceptable.

7.1.7. Treatment Compliance

Study drug will be administered at the study center. To ensure treatment compliance, administration of the study drug will be supervised by the Investigator or authorized designee. Compliance will be further confirmed by bioanalytical assessment of ATYR1923 in serum samples (see Section 8.4).

8. STUDY VISITS AND ASSESSMENTS

8.1. Schedule of Assessments

The Schedule of Assessments is presented in Table 1.

8.2. Screening and Baseline Measurements

8.2.1. Informed Consent

All patients or their designated legal representatives must provide informed consent, based on local age of majority, before any samples are collected or evaluations performed in this study that are not part of standard patient care.

8.2.2. Demographics

Patient demographics, including age, sex, and race, are to be documented during Screening.

8.2.3. Medical History and History of COVID-19 Symptoms

A complete medical history, including respiratory history, is to be documented during Screening. Smoking history of use of any inhalation products (eg, nicotine-containing products including e-cigarettes or e-vaporizers) is to be documented.

COVID-19 symptom history is to include date of onset of symptoms, list of symptoms (eg, fever, fatigue cough [with or without sputum production], anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, headache, diarrhea, nausea, vomiting, pneumonia, loss of taste and/or smell), and radiological test results.

The date of initial SARS-CoV-2 positivity also is to be documented, if available.

8.2.4. SARS-CoV-2 Testing

Confirmation of SARS-CoV-2 infection by PCR is to be performed during Screening. However, if the test was performed at the study center/institution within 7 days before Day 1 and results are available in the medical record, then this test may be used as the confirmatory screening test. If the SARs-CoV-2 test results are older than 7 days from Day 1 or the test was performed at a different location, a repeat test is to be performed.

After Screening, nasopharyngeal swab results are to be recorded in the eCRF per SOC until discharge. If quantitative testing is performed, the results also are to be recorded in the eCRF.

8.2.5. Serology

A blood sample for serology, including HIV1 and 2, HBsAg, and anti-HCV, is to be collected during Screening within 7 days before Day 1 and tested locally. If serology is positive for HCV, the Investigator may elect to measure HCV ribonucleic acid to confirm the absence of infection.

Patients with positive results are not eligible for study participation.

8.2.6. Height and Weight

Height is to be documented during Screening; height may be documented via patient report.

Weight is to be measured within 3 days predose; weight is to be used to calculate the study drug dose.

If there is a weight change >10% between Day -3 and Day 1, the dose should be recalculated.

8.3. Efficacy and Exploratory Assessments

8.3.1. Hospitalization Status

The date, time and reason of initial hospitalization and discharge are to be documented in the eCRF. During hospitalization, the date and time of any change in the patient's hospitalization status, specifically admittance and discharge to the intensive care unit are also to be recorded. If, in the Investigator's opinion, the patient required a higher level of care (ie, admittance to the intensive care unit) but did not receive due to resource availability, this should be documented.

8.3.2. WHO Ordinal Scale of Clinical Status

The patient's clinical status is to be assessed using the WHO Ordinal Scale (see Appendix 1) at the time points designated in Table 1. The WHO Ordinal Scale score is to be determined between 06:00 and 10:00 hours each day, or per local SOC, and the score closest to 8:00 hours recorded.

The date and time of any change in the components of clinical status are to be documented in the patient's eCRF, including:

- Change in ambulatory status.
- Requirement for oxygen (yes/no), and if yes, method of oxygenation (mask/nasal prongs, non-invasive ventilation, or high-flow oxygen; intubation and mechanical ventilation). The volume of oxygen administered is to be captured as a concomitant medication (see Section 7.1.6). If, in the Investigator's opinion, a patient required a higher level of oxygenation, but did not receive due to resource availability, this should be documented.

8.3.3. Pulse Oximetry

To assess eligibility, one measurement of SpO_2 without supplemental oxygen should be attempted. If not clinically feasible, obtain the measurement with supplemental oxygen. The corresponding level of supplemental O_2 use is to be recorded in the eCRF at screening to confirm eligibility.

On Day 1, SpO_2 readings will be recorded pre-dose then at 1 and 4 hours (±15 minutes) after the start of infusion (SOI).

After Day 1, SpO_2 is to be measured per SOC and recorded in the eCRF, as per Table 1.

8.3.4. Vital Signs and Temperature

Vital signs include blood pressure, heart rate, and respiration rate, and temperature.

Day1 vital signs are to be obtained pre-infusion and at 15 and 30 minutes (±5 minutes) and at 1, 2, and 4 hours (±15 minutes) after the start of infusion (SOI). Vital signs will include blood pressure (systolic and diastolic), heart rate, and respiratory rate, recorded after resting for 5 min.

After Day 1, temperature and vital signs are to be measured per SOC and recorded in the eCRF, as per Table 1.

8.4. Pharmacokinetic Measurements and Variables

At the time points defined in the Schedule of Assessments (Table 1), blood samples will be taken for the PK analysis of ATYR1923 in serum samples and analyzed at a central laboratory. The exact times of blood sampling will be recorded in the eCRF.

Details on sample collection, handling, storage and shipping of blood samples for PK analysis of ATYR1923 will be described in the Laboratory Manual.

8.5. Pharmacodynamic/Exploratory Measurements and Variables

8.5.1. Blood for Cytokines/Chemokines

Blood samples for the analysis of cytokines/chemokines, including C-reactive protein, INF-γ, IL-6, IL-2, IL-7, IL-10, TNFα, MIP1, CXC-10, and MCP-1 will be taken at the time points designated in Table 1 and analyzed at a Central Laboratory.

Details on sample collection, handling, storage and shipping of blood samples for cytokines/chemokines analysis will be described in the Laboratory Manual.

8.6. Safety and Tolerability Measurements

Safety assessments will be performed in accordance with the Schedule of Assessments.

8.6.1. Physical Examination

If performed at the study center/institution within 7 days before Day 1 and results are available in the medical record, any abnormal physical examination findings are to be documented in the eCRF. Any abnormal physical examination findings from examinations performed per SOC through discharge are to be recorded in the eCRF.

Respiratory findings supportive of severe respiratory distress, if present, are to be documented on the Physical Examination eCRF if not otherwise captured as part of the patients recent COVID-19-related medical history.

8.6.2. Immunogenicity Measurements

Blood samples for determination of Jo-1 Ab levels in serum will be collected at the time points designated in Table 1 and processed at the local laboratory. Any patient who develops positive Jo-1 antibodies will be monitored clinically for signs/symptoms of anti-synthetase syndrome.

Blood samples for determination of ADAs against ATYR1923 in serum will be collected at the time points designated in Table 1 and analyzed at a central laboratory.

In addition, blood samples for ADAs and Jo-1 Ab levels in serum will be repeated if the patient experiences a suspected IRR or anaphylaxis per Section 9.9.

Blood samples will be collected and processed as described in the Laboratory Manual. The exact times of blood sampling will be recorded in the eCRF.

8.6.3. Adverse Events

AEs will be recorded from the time of initiation of study drug administration through the last visit for a patient. Any clinically significant observations in results of clinical laboratory, 12-lead electrocardiograms (ECGs) (if performed per SOC), vital signs, pulse oximetry, or physical examinations are to be recorded as part of the patient's medical history if occurring prior to start of dosing and as an AE if occurring after the start of study drug administration at Day 1, where the finding represents a change from Baseline.

A TEAE is defined as any event not present prior to (the first) administration of the study drug or any event already present that worsens in either intensity or frequency following exposure to the study drug.

An AE which occurs prior to (the first) administration of the study drug will be considered a pre-treatment AE.

AEs that occur during or within 24 hours after study drug injection should be captured as individual signs and symptoms (eg, dyspnea, rash, flushing) rather than a diagnosis of allergic reaction or IRR.

Patients will be asked non-leading questions and evaluated to determine the occurrence of AEs. All AEs reported or observed spontaneously during the course of the study will be recorded.

The intensity of each AE will be rated by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 (available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

AEs not listed on the NCI CTCAE V5.0 are to be rated by the Investigator as "mild (Grade 1)", "moderate (Grade 2)", "severe" (Grade 3), "life-threatening"(Grade 4), or "fatal" (Grade 5).

The relationship between the AEs and the study drug will be indicated as "not related", "unlikely related", "possibly related", or "related". AEs assessed as "possibly related" or "related" will be considered to be related to the study drug whereas AEs assessed as "not related" or "unlikely related" will be considered not to be related to the study drug.

Details on the rating of the severity of the AEs and relationship to the study treatment are given in Section 9.2.

8.6.3.1. Infections

Any new infections are to be documented as AEs. The new infection site and source of culture are to be recorded in the eCRF.

8.6.4. Concomitant Medications

Medications that are ongoing at Screening are to be documented. Furthermore, all medications and supplements, including supplemental oxygen, the patient receives during their course of hospitalization as part of their standard of care as well as during the study are to be documented in the source documents and in the eCRF.

8.6.5. Safety Laboratory Tests

Blood and urine samples for clinical safety laboratory assessments will be collected at the time points designated in Table 1 at Screening and Day 1. After Day 1, clinical safety laboratory assessments are to be collected per SOC. Note that if screening safety laboratory assessments are performed within 2 days of Day 1, then the pre-dose Day 1 safety laboratory assessments need not be repeated.

These samples will be analyzed at the local laboratory following their laboratory standard operating procedures (SOPs).

The following parameters may be collected and documented in the eCRF, as available per SOC:

- Clinical chemistry (serum quantitatively):
- Total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase, albumin, creatinine, blood urea nitrogen, total protein, glucose, , sodium, potassium, calcium and chloride,.
- Hematology (blood quantitatively):
  - Leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes, partial automated differentiation (lymphocytes, monocytes, eosinophils, basophils, neutrophils), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration
- Coagulation (blood quantitatively):
  - Prothrombin time (reported in seconds and as international normalized ratio) and partial thromboplastin time
- Urinalysis (semi-quantitative by dipstick):
  - Hemoglobin, urobilinogen, ketones, glucose, protein
  - Microscopy is to be performed if indicated by an abnormal and clinically significant result. Culture results, if conducted per SOC, are to be documented.

- Cardiac troponins, ferritin, B-type natriuretic peptide (BNP) or N-terminal-pro-BNP, and D-dimer.

In case of unexplained or unexpected clinical laboratory test values, the tests will be repeated as soon as possible and followed up until the results have returned to the normal range, baseline level and/or an adequate explanation for the abnormality is found. The clinical laboratory will clearly mark all laboratory test values that are outside the normal range and the Investigator will indicate which of these deviations are clinically significant. These clinically significant deviating laboratory results will then be recorded as AEs and the relationship to the treatment will be indicated (see also Section 9.2).

8.6.6. Radiographic Studies and Electrocardiograms

A radiologic study performed within 7 days prior to Day 1 is acceptable to determine study eligibility. If the radiologic study was performed >7 days before Day 1, a repeat radiologic study is to be performed during Screening.

An ECG is to be collected during Screening if it was performed per SOC.

Findings from any radiographic studies or ECGs performed during inpatient hospitalization are to be recorded in the eCRF. Radiographic images may be collected and may be submitted to a central reader for review.

8.6.7. Pregnancy Testing

Female patients of childbearing potential must have a urine pregnancy test performed during Screening. Any patient with a positive pregnancy test result is not eligible for study participation. Pregnancy test results are to be obtained and confirmed to be negative prior to randomization and study drug infusion.

8.6.8. Appropriateness of Measurements

The assessments, which will be made in this study are standard, and generally recognized as reliable, accurate, and relevant. Efficacy assessments are consistent with the WHO, COVID-19 Therapeutic Trial Synopsis.

9. ADVERSE EVENTS

9.1. Definitions

9.1.1. Adverse Event

An AE is defined in the ICH Guideline for GCP as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment" (ICH E6:1.2).

Worsening of a pre-existing medical condition, (ie, diabetes, migraine headaches, gout) is to be considered an AE if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Interventions for pretreatment conditions (ie, elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered AEs.

In the case of death, only record "Fatal" for the event causing death. AEs that are ongoing at the end of the study or time of death are to be noted as "continuing."

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual patient represents a significant change from baseline. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) should not be recorded as AEs; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered AEs.

9.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug Application (IND) safety reporting, "reasonable possibility" and/or at least possibly related means there is evidence to suggest a causal relationship between the drug 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 drug.

9.1.3. Serious Adverse Event

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- is fatal.

  For the purposes of this study, death due to SARS-CoV2 infection is not considered an SAE.

- is life-threatening (ie, places the patient at immediate risk of death).

- requires in-patient hospitalization (overnight stay) or prolongation of existing hospitalization.

  As all patients are required to be hospitalized as inpatients to be eligible for this study, any event other than SARS-CoV2 infection requiring prolonging of inpatient hospitalization and/or rehospitalization after discharge will be considered an SAE. Hospitalization due to SARS-CoV2 infection is not considered an SAE, provided that it did not deteriorate in an unexpected manner during the study.
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- is an important medical event; an important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.1.4. Unexpected Adverse Event

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or intensity that has been previously observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the current application, as amended.

9.1.5. Serious and Unexpected Suspected Adverse Reaction

A SUSAR is any event that meets all 3 of the following definitions:

1) suspected adverse reaction (Section 9.1.2);

2) serious (Section 9.1.3); and

3) unexpected (Section 9.1.4).

9.2. Adverse Event Assessment

All AEs will be collected and recorded in this study from the time of initiation of study drug administration through the last visit for a patient. This includes AEs the patient reports spontaneously, those observed by the Investigator, and those elicited by the Investigator in response to open-ended questions during scheduled study center visits.

AEs that occur during or within 24 hours after study drug infusion are to be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or IRR.

Each AE is to be assessed by the Investigator with regard to the following categories.

9.2.1. Serious/Non-Serious

AEs that meet the criteria specified in Section 9.1.3 are to be considered serious.

9.2.2. Relationship to Study Drug

This determination is based on the Investigator's clinical judgment regarding the likelihood that the study drug caused the AE and may include consideration of some or all of the following factors:

- Alternative possible causes of the AE, including the patient's underlying disease or co-morbid conditions, other drugs, other host and environmental factors;
- The chronological relationship between the exposure to study drug and the AE;
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study drug;
- Whether the AE resolved or improved with decreasing the dose or stopping the study drug (ie, dechallenge);

Whether the AE recurred or worsened with re-exposure to the drug (ie, rechallenge).

The relationship between the study drug and the AE will be described using one of the following categories Table 2.

Table 2: Criteria for Determination of Adverse Event Relationship to Study Drug

Relationship	Definition
Related	The study drug is more likely the cause of the AE than other factors
Possibly Related	There is a reasonable possibility that the study drug is the cause of the AE, including that the study drug and another factor(s) are equally likely as causes of the AE
Unlikely Related	Another factor is considered more likely the cause of the AE than the study drug
Not related	Another factor is considered to be the cause of the AE

9.2.3. Relationship to SARS-CoV2 infection:

The relationship between each AE and SARS-CoV2 infection (related/unrelated) is to be documented.

9.2.4. Intensity

The intensity of each AE is to be assessed by the Investigator using the NCI CTCAE, version 5.0 (available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

AEs not listed on the NCI CTCAE V5.0 are to be rated by the Investigator according to the categories in Table 3.

Table 3: Criteria for Determination of Adverse Event Intensity

Intensity	Definition
Mild (Grade 1):	Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated.
Moderate (Grade 2)	Minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Severe (Grade 3):	Severe or medically significant but not immediately life threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; incapacitating with inability to work or perform normal daily activity.
Life-threatening (Grade 4):	Consequences: urgent intervention indicated.
Fatal (Grade 5)	AE resulted in death

9.2.5. Outcome

The outcome of each AE will be described using the categories in Table 4.

Table 4: Criteria for Determination of Adverse Event Outcome

Outcome	Definition
Resolved without sequelae:	The event resolved and patient returned to baseline
Resolved with sequelae:	The event resolved but the patient is left with residual problems (eg, functional deficits, pain)
Resolving	At the last observation, the event was improving
Not Resolved	At the last observation, the event was unchanged
Death (Fatal)	To be used for the one AE which, in the judgment of the Investigator, was the primary cause of death
Unknown	There were no observations after the onset (initial observation or report) of the event

9.2.6. Study Drug Action

For each AE, the Investigator will indicate the action taken regarding the administration of study drug per the categories in Table 5.

Table 5: Study Drug Action Taken as a Result of Adverse Events

Action	Definition
Discontinued (withdrawn)	Study drug was stopped permanently due to the AE
Dosing Interrupted	Study drug regimen was modified by being temporarily halted, but drug was not stopped permanently
Dose Decreased	Study drug regimen was modified by subtraction, ie, by decreasing the strength or amount
Dose Increased	Study drug regimen was modified by addition, ie, by increasing the strength or amount
None	No change in the administration of study drug

9.3. Recording Adverse Events

All AEs occurring from the time of initiation of study drug administration through the last follow-up visit, or after the end of the study, if thought to be related to study drug, are to be recorded in the source documents and in the eCRF. All AE reports are to contain the following details regarding the AE: a brief description, onset date and time, resolution date and time, intensity, treatment required, relationship to study drug, action taken with study drug, outcome, and whether the event is classified as serious.

AEs that occur during or within 24 hours after study drug injection should be captured as individual signs and symptoms (eg, dyspnea, rash, flushing) rather than a diagnosis of allergic reaction or IRR.

9.4. Reporting Serious Adverse Events

SAEs will be collected and recorded throughout the study period, beginning with the signing of the informed consent form (ICF) through the last follow-up visit, or after the end of the study if thought to be related to study drug.

The Investigator must report all SAEs within 24 hours of discovery to the Contract Research Organization (CRO) Safety Team.

SAE reporting, including supporting materials, will be performed by the study center personnel using a system approved by the Sponsor. Detailed training will be provided by the CRO. Contact information for guidance and assistance with SAE reporting is provided in the Study Reference Manual. A completed SAE report is to be entered into the system approved by the Sponsor within 24 hours of discovering the event. Upon entry into the system, the responsible parties (including Medical Monitor and Safety Reporting Specialist) will be immediately notified.

The Study Reference Manual will include an emergency back-up paper based reporting system, to be used if needed.

The CRO Safety Team will immediately (within one business day of receipt) forward the SAE report to the Sponsor. The initial report should include at least the following information:

- Patient's identification number;
- Description and date of the event;
- Criterion for serious; and
- Preliminary assignment of causality to study drug.

The Medical Monitor may contact the Investigator via telephone for urgent follow-up information regarding the SAE, as appropriate.

The Investigator, or designated party, should notify the appropriate IRB of SAEs occurring at the study center and other AE reports received from aTyr, in accordance with local procedures and statutes.

SAEs that are considered as possibly or definitely related to the investigational product, and as unexpected (ie, SUSARs), will be reported to the National Regulatory Authority(ies) and IRB by the Sponsor or Sponsor's designee as required by applicable local regulations. Per regulation, any fatal or life-threatening SUSAR will be reported to the National Regulatory Authority(ies)/IRB within 7 calendar days, and additional information within an additional 8 calendar days. The Sponsor or Sponsor's designee is required to submit any other SUSAR to the National Regulatory Authority(ies)/IRB within 15 calendar days of notification. The Sponsor or its designee is also responsible for notifying the investigational sites of all expedited SAEs, in

accordance with local requirements. The Investigator must keep copies of all expedited SAE information including correspondence with the Sponsor on file.

9.5. Follow-Up of Adverse Events

The Investigator must continue to follow all study drug-related TEAEs either until resolution or the Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study and may be conducted by telephone contact or unscheduled visit.

9.6. Reporting Safety Information

The Investigator must promptly report to his or her IRB all unanticipated problems involving risks to patients, in accordance with local requirements. This may include death from any cause and all SAEs reasonably or possibly associated with the use of study drug according to the IRB's procedures.

9.7. Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis and only in the event of an emergency. The Investigator or other physician in attendance in such an emergency must contact the Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The Medical Monitor, in conjunction with the Investigator, will decide whether the patient should continue to participate in the study. All protocol deviations and reasons for such deviations must be noted in the eCRF.

9.8. Pregnancy

Pregnancies occurring while the patient is receiving study drug or within 30 days after the patient's last dose of ATYR1923 will not be considered serious, but are to be reported using the same procedures as for SAEs described in Section 9.4.

In the event of a pregnancy, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the patient until completion of the pregnancy, and must notify the Medical Monitor of the outcome within 5 days. The Investigator will provide this information as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such. Furthermore, all neonatal deaths that occur within 30 days of birth are to be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported.

9.9. Management of Potential Infusion Related Reactions, Including Anaphylaxis

ATYR1923 is a biologic and as with all biologics there is a risk for IRRs. These reactions typically occur in close temporal relationship with the infusion. They may be related to cytokine release or immune mediated.

A generalized IRR could be occurring when any symptoms begin during the study drug infusion or during the post-infusion observation period. While these symptoms may be self-limiting, such symptoms may signal the possibility of a severe reaction that could escalate into a life-threatening situation.

Should a patient develop an IRR the subsequent management will depend on the nature of the IRR. Where the IRR symptoms are not cardiorespiratory in nature i.e. they comprise cutaneous rash, flushing, burning sensation etc. and are mild to moderate in intensity – the patient may complete the infusion and receive subsequent doses. The patient will need to be observed until all symptoms resolve or for 6 hours after the end of the infusion.

If the IRR symptoms constitute a cardiorespiratory risk (hypotension, dyspnea, hypoxia etc.) or any severe AE then all further dosing should be stopped for the patient. If necessary, the patient should be transferred to an acute care facility.

Vital signs, pulse oximetry, and ECGs are to be performed to gather clinical information as soon as possible after the onset of clinical symptoms of a generalized IRR (for instance, immediately after cessation of the study drug infusion if such a reaction is seen) and monitored as medically indicated. ECGs should be repeated as medically indicated.

The following tests and procedures are to be performed 1 to 2 hours after the onset of symptoms:

- ATYR1923 serum concentrations.
- Jo-1 and ADA.
- Tryptase.
- Complete safety laboratory panel, including urine analysis and urine microscopy.
- Cytokines/chemokines.

The Investigator must inform the study Medical Monitor promptly regarding any patient who experiences a generalized IRR for additional instruction.

Patients who experience generalized IRRs will continue to be monitored / have repeat assessments performed at a schedule determined by the Investigator in consultation with the Medical Monitor and Sponsor. Appropriate follow up for the patient must occur to ensure that there are no late-occurring sequelae.

Note that in the eCRF, AEs that occur during or within 24 hours after study drug injection should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or IRR.

9.9.1. Anaphylaxis

IRRs meeting the definition of anaphylaxis are to be reported in the eCRF as such (Sampson et al., 2006):

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

   And at least one of the following:

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).

   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).

   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).

   c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).

   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

   a. Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure*.

   b. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

Patients who experience anaphylaxis are to be managed as described in Section 9.9.

10. STATISTICAL ANALYSES

10.1. Statistical Procedures and Determination of Sample Size

10.1.1. Analysis Sets

10.1.1.1. Intent-to-Treat Set

The Modified Intent-to-treat Set will comprise all patients randomized who have received any amount of study drug. Patients will be analyzed as randomized.

10.1.1.2. Safety Set

The Safety Set will comprise all patients who have received any amount of study drug. Patients will be analyzed as treated.

10.1.2. Statistical and Analytical Plan for Pharmacokinetic, Pharmacodynamic, Safety and Exploratory Evaluation

A Statistical Analysis Plan (SAP) will be generated by the CRO Biostatistics Department; the SAP will be finalized prior to database lock or interim analysis if applicable and subsequent unblinding of study treatment codes. Full details of the analysis to be performed will be included in the SAP.

Any deviation from the SAP will be reported in the section "Changes in Planned Analysis" in the CSR.

10.1.2.1. Pharmacokinetic Evaluation

The PK parameters and their statistical evaluation will be included in the Clinical Study Report (CSR) for this study.

All data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form. Any additional analyses will be specified in the SAP.

10.1.2.2. Efficacy Evaluation

The efficacy parameters and their statistical evaluation will be included in the CSR of this study.

All data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

10.1.2.3. Evaluation of Safety and Tolerability

Safety and tolerability will be assessed through AEs, clinical laboratory, vital signs, ECGs and physical examination findings, and any other parameter that is relevant for safety assessment.

10.1.2.3.1. Adverse Events

A listing of all individual AEs will be provided. Summary tables of TEAEs will be presented by system organ class based on the Medical Dictionary for Regulatory Activities (MedDRA) terminology list (preferred terms): 1 containing the number of TEAEs (frequency of occurrence, number of patients experiencing the event) by treatment and 1 containing the number of drug-related TEAEs (frequency of occurrence, number of patients experiencing the event) per treatment. Additional tables of total counts by treatment and relationship and by treatment and intensity will be given.

10.1.2.3.2. Clinical Laboratory

Clinical laboratory data will be listed, and will also be flagged if the parameter is outside the reference range. A summary of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively, where applicable.

10.1.2.3.3. Immunogenicity

The presence of ADAs and Jo-1 antibodies in serum will be listed and presented descriptively, where applicable.

10.1.2.4. Evaluation of Efficacy and Exploratory Variables

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage (n, %) of patients within each classification. Details regarding efficacy and exploratory analyses, including the handling of missing variables, will be detailed in the SAP.

10.1.3. Determination of Sample Size

For this study, no prospective calculations of statistical power have been made. The sample size has been selected to provide information on safety, tolerability, PK and efficacy following single doses of ATYR1923. Any p-values to be calculated according to the SAP will be interpreted in the perspective of the explorative character of this study.

10.2. Data Quality Assurance

The study may be audited to assess adherence to the clinical study protocol and Quality System. During the conduct of the study, process-related audits may be performed. An audit certificate will be provided in the appendices of the final CSR outlining any audits and other related activities performed.

The clinical research site will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study will be conducted according to the relevant

regulatory requirements. The eCRF entries will be verified with the source documentation, if applicable (in some cases there are no source pages, therefore verification is not necessary).

Regulatory authorities, the IRB and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study. Review procedures will be followed by the Sponsor and designees for all documents that are generated in relation with the study. Essential study activities of personnel will be checked by colleagues during execution, and each of them will sign off the documentation for execution or checking of the activities.

An explanation will be given for all missing, unused and spurious data in the relevant sections of the CSR.

10.2.1. Interim Analyses

Details of any interim analyses will be provided in the SAP.

10.3. Changes to the Planned Statistical Methods

Changes to the planned statistical methods will be documented in the CSR.

11. ETHICAL, LEGAL, AND ADMINISTRATIVE CONSIDERATIONS

11.1. Good Clinical Practice

This study will be conducted according to the protocol and in compliance with ICH GCP, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

The Investigator confirms this by signing the protocol.

11.2. Informed Consent

Informed consent, based on age of majority, in compliance with 21 Code of Federal Regulations § 50 and/or ICH regulations will be obtained from each patient or their designated legal representative prior to undergoing any protocol-specific tests or procedures that are not part of routine care.

The Sponsor or designee will provide an ICF template to the Investigator for use in developing a study center-specific consent document. Prior to submission of the study center-specific ICF form to the IRB, these documents must be reviewed and approved by the Sponsor or designee. Any changes requested by the IRB must also be approved by the Sponsor or designee. The final IRB-approved ICF must be provided to the Sponsor or designee. Revisions to the ICF required during the study must be approved by the Sponsor or designee, and a copy of the revised ICF provided to the Sponsor or designee.

Before recruitment and enrollment, each prospective patient or their designated legal representative will be given a full explanation of the study and be allowed to read the ICF in a language they understand. After the Investigator or designee is assured that the patient/patient's designated legal representative understands the commitments of participating in the study, the patient/patient's designated legal representative, as appropriate, will be asked to provide consent.

If able, a signed and dated ICF will be maintained in the patient's medical record. However, due to the nature of SARS-CoV-2 infection, specific site informed consent policies will be followed and a physical copy of the signed consent form may not be retained.

11.3. Institutional Review Board/Independent Ethics Committee

Federal regulations and ICH require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to the study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment and any other written information regarding this study to be provided to a patient must be approved by the IRB.

All IRB approvals must be dated and signed by the IRB Chairperson or designee and must identify the IRB by name and address, the clinical protocol by title and/or protocol number, and the date approval or favorable opinion was granted for the clinical research.

No drug will be released to the site to dose a patient until written IRB authorization has been received by the Sponsor or designee.

The Investigator is responsible for obtaining continuing review of the clinical research at least annually or more often if specified by the IRB. The Investigator must supply the Sponsor or designee with written documentation of the approval of the continued clinical research.

The Investigator, sponsor, or designee as applicable, will make all attempts to ensure that the IRB is constituted and operates in accordance with Federal and ICH GCP and any local regulations.

11.4. Amending the Protocol

Any changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor or designee and the IRB that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB for approval prior to patients being enrolled into the amended protocol.

The Sponsor may make administrative changes (ie, changes that do not significantly affect patient safety or the study's scope or scientific quality) without any further approvals.

All amendments will be distributed to all protocol recipients.

11.5. Confidentiality/Data Protection

All study findings and documents will be regarded as confidential. The Investigator and other study personnel must not disclose such information without prior written approval from the Sponsor.

Patients will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the participant identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

11.6. Publication Policy

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. The initial planned publication will be a multi-center report of the study outcome. Additional publications from a given center can only occur after the publication of the multi-center results. A prepublication manuscript is to be provided to the Sponsor at least 30 days prior to the submission of the manuscript to a publisher.

Similarly, the Sponsor will provide any company-prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher.

12. STUDY MANAGEMENT

12.1. Data Quality Assurance

The Sponsor or its designated legal representative will conduct a study center visit to verify the qualifications of each Investigator, inspect study center facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

12.2. Case Report Forms and Source Documentation

The Investigator and designees agree to maintain accurate eCRFs and source documentation as part of case histories. Source documents are the originals of any documents used by the Investigator or subinvestigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the study.

The Sponsor or designee will provide eCRF access to the study center. eCRFs will be completed for each patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of informed consent, study procedures, AEs, and patient status.

The Investigator, or designated legal representative, should complete the eCRF as soon as possible after information is collected / data are available, preferably on the same day that a patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

12.3. Monitoring

A clinical research associate (CRA) or other representative of the Sponsor or designee will verify the qualifications of each Investigator, confirm the appropriateness of study center facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

During the course of the study, the CRA will review protocol compliance, compare eCRFs and individual patient medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements in respect to GCP. eCRFs will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

12.4. Inspections

Regulatory authorities and/or quality assurance personnel from the Sponsor or its designated representative may wish to carry out such source data checks and/or in-center audit inspections. The Investigator assures the Sponsor of the necessary support at all times. In the event of an

audit, the Investigator agrees to allow the Sponsor's representatives and any regulatory agencies access to all study records.

12.5. Financial Disclosure Reporting Obligations

Investigators and subinvestigators are required to provide financial disclosure information to the sponsor to permit the sponsor to fulfill its regulatory obligation. Investigators and subinvestigators must commit to promptly updating the information if any relevant changes occur during the study and for a period of one year after the completion of the study.

12.6. Archiving Study Records

Essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local requirements.

ICH requires that patient identification codes be retained for at least 15 years after the completion or discontinuation of the study.

13. REFERENCES

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14. APPENDICES

Appendix 1: WHO Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Source: WHO R&D Blueprint novel Coronavirus. COVID-19 Therapeutic Trial Synopsis. Available at: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf