NCT #: NCT03824392

aTyr Pharma, Inc.

A Randomized, Double-Blind, Placebo-Controlled Multiple Ascending Dose Study of Intravenous ATYR1923 in Patients with Pulmonary Sarcoidosis

Protocol Number: ATYR1923-C-002

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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Contract Research Organization:	Axiom Real-Time Metrics 1 City View Drive Toronto, Ontario M9W1J1 Canada
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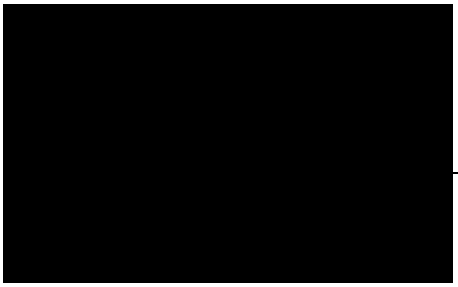
SPONSOR SIGNATORY



25 September 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)/Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of aTyr and the IRB/IEC, 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

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Multiple Ascending Dose Study of Intravenous ATYR1923 in Patients with Pulmonary Sarcoidosis
Protocol Number:	ATYR1923-C-002
Study Phase:	1b/2a
Investigators / Study Centers:	This multicenter study will be conducted at approximately 18 study centers globally.
Study Objectives:	**Primary** • To evaluate the safety and tolerability of multiple ascending intravenous (IV) doses of ATYR1923 in patients with pulmonary sarcoidosis. **Secondary** • To assess the potential steroid-sparing effect of multiple ascending doses of ATYR1923 in patients with pulmonary sarcoidosis. • To assess the potential immunogenicity of multiple ascending IV doses of ATYR1923 in patients with pulmonary sarcoidosis. • To characterize the pharmacokinetics (PK) of multiple ascending IV doses of ATYR1923 in patients with pulmonary sarcoidosis. **Exploratory** • To explore the preliminary efficacy of multiple ascending IV doses of ATYR1923 in patients with pulmonary sarcoidosis by evaluating changes over time in: – Disease activity (pulmonary parenchymal inflammation), assessed by ^{18}F-fluorodeoxyglucose positron-emission tomography combined with computed tomography (^{18}F-FDG-PET/CT) (optional). – Lung function, assessed by percent predicted forced vital capacity (FVC%) and diffusing capacity of the lungs for carbon monoxide (DL_{CO}). – Serum biomarkers, including angiotensin converting enzyme (ACE), soluble IL-2 receptor (sIL-2R), extracellular histidyl-tRNA-synthetase, neuropilin 2 (NRP2), and vascular endothelial growth factor C (VEGFC).

- State of immune cell anergy in peripheral blood mononuclear cells (PBMCs)
- Health-related quality of life scales, including the Sarcoidosis Assessment Tool (SAT), King's Sarcoidosis Questionnaire (KSQ), Leicester Cough Questionnaire (LCQ), Fatigue Assessment Scale (FAS), and the self-administered computerized Baseline/Transitional Dyspnea Indices (SAC BDI-TDI).
- Skin lesions, for patients with cutaneous disease involvement at baseline, as assessed by Skin Physician Global Assessment (SPGA), body surface area (BSA) assessment, and the Sarcoidosis Activity and Severity Index (SASI; on a target lesion), as well as serial biopsies of non-target lesion(s) (optional at select sites).

Study Design:

This randomized, double-blind, placebo-controlled, study will evaluate the safety, tolerability, immunogenicity, PK, and preliminary efficacy of multiple ascending doses of IV ATYR1923 in patients with pulmonary sarcoidosis undergoing a protocol-guided oral corticosteroid (OCS) tapering regimen.

This study will consist of 3 staggered multiple dose cohorts. Each eligible patient will participate in only one cohort during the study. Within each cohort, 12 patients will be randomized 2:1 (block size of 6) to ATYR1923 (N=8) or placebo (N=4). Study drug will be administered via IV infusion every 4 weeks for a total of 6 doses (20 weeks of treatment). The follow-up study visit is scheduled for 4 weeks after the last infusion. The ATYR1923 doses levels to be evaluated are 1.0 mg/kg, 3.0 mg/kg, and 5.0 mg/kg.

Day 1 is the calendar day of first infusion.

Starting on Day 15, patients will begin a taper (reduction) in OCS (per the ATYR1923-C-002 Oral Corticosteroid Taper Guidelines) from their starting dose of 10-25 mg/day of prednisone (or equivalent) to a target dose of 5 mg/day, to be completed on or before Day 50. The OCS dose will be tapered by 5.0 mg/day every 1 to 2 weeks, depending on the starting dose. Smaller incremental titrations to the target dose of 5 mg/day by Day 50 may be implemented per Investigator judgement. Patients will be maintained at the target dose of 5.0 mg/day (or equivalent) through Week 24/End-of-Study (EOS). Optionally, further titrations in the OCS dose to below 5 mg/day may be attempted after the Week 16 visit, if determined by the Investigator to be feasible.

Patients who develop an acute worsening of symptoms or are unable to adhere to the protocol-defined OCS tapering regimen may receive 'rescue' treatment with higher OCS doses as clinically indicated. Upon resolution of symptoms, the Investigator may choose to reinstitute a taper back down to the target maintenance dose of 5 mg/day. Patients

who require rescue treatment following two attempts at tapering to 5 mg/day may remain on a higher stable dose of OCS as determined by the Investigator. Patients who require an increase in OCS dose at any time in the study should continue to receive blinded study drug and followed through to the end of the study. It is planned that 36 patients with pulmonary sarcoidosis will be randomized into one of 3 sequential cohorts, each comprising 12 patients allocated 2:1 (block size of 6) to ATYR1923:Placebo.

Planned Dose Cohorts

The planned dose cohorts are as follows:

Cohort	Dose (mg/kg)	# of Doses	Dosing Frequency	N	Ratio ATYR1923: Placebo
1	1.0	6	Every 4 weeks	12	2:1
2	3.0	6	Every 4 weeks	12	2:1
3	5.0	6	Every 4 weeks	12	2:1

Safety Monitoring

Ongoing review of blinded safety and tolerability data will be performed by the Medical Monitor and aTyr Pharma personnel.

An independent Data Safety Monitoring Board (DSMB) will perform interim reviews of unblinded safety, tolerability, and immunogenicity data to review and approve dose escalation to the next highest dose cohort (see *Dose Escalatio*n) and ad hoc as per Sponsor request if a pattern of unexpected, clinically significant trends or changes in other safety assessments is identified through blinded safety data reviews.

Dose Escalation

Cohorts 1 through 3 will be enrolled sequentially in a staggered manner. After at least 6 patients of a given cohort have received at least 3 infusions of study drug (ATYR1923 or placebo), cumulative unblinded safety data (including but not limited to any reported adverse events (AEs), electrocardiogram (ECG) recordings, clinical laboratory values and vital signs) will be reviewed by the DSMB. Enrollment in the next scheduled (higher dose) cohort may commence after this review is completed, dose escalation is approved, and the remaining 6 patients have been randomized in the previous cohort. Dose escalation will continue in this manner until the highest planned dose level of ATYR1923 is reached, or the criteria for pausing enrollment have been met.

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 an ongoing cohort, stopping further dose escalation, continuing the study as planned, or continuing the study with modifications, such as evaluation of a lower or intermediate dose in the next cohort(s) to gain more information on safety and tolerability. In addition, if unexpected, clinically significant trends or changes in other safety assessments are identified during routine blinded safety reviews the Sponsor may request the DSMB to similarly perform an unblinded review and provide recommendations.
Number of Patients Planned:	It is planned that 36 adult patients with pulmonary sarcoidosis will be randomized into one of 3 sequential cohort. Patients who withdraw for reasons other than treatment-related AEs may be replaced at the discretion of the Sponsor.
Diagnosis and Main Criteria for Inclusion:	**Inclusion Criteria** The following inclusion criteria must be met for a patient to be eligible for inclusion in the study: 1. Male or female patients aged ≥18 to ≤75 years inclusive at time of informed consent 2. Diagnosis of pulmonary sarcoidosis for ≥6 months (cutaneous and ocular involvement allowed), defined as: • Histologically proven diagnosis of sarcoidosis by bronchoscopy, biopsy (any organ) or bronchioalveolar lavage. • Evidence of parenchymal lung involvement by historical radiological evidence (eg, computed tomography [CT], magnetic resonance imaging [MRI], ^{18}F-FDG PET/CT or chest X-ray) or on the Screening ^{18}F-FDG PET/CT. 3. Must have symptomatic and/or active pulmonary sarcoidosis as evidence by: • Clinical findings of dyspnea, as indicated by a Modified Medical Research Council (MRC) Dyspnea Scale grade of at least 1; and • FVC% predicted ≥50%. 4. Must be receiving treatment with 10 to 25 mg/day of oral prednisone (or oral equivalent; eg, methylprednisolone), at a stable dose for ≥4 weeks prior to Day 1, and be determined by the Investigator to be capable of undergoing the protocol-specified steroid taper regimen.

- Treatment with one oral immunomodulatory therapy (eg, methotrexate, azathioprine, hydroxychloroquine) at a stable dose for ≥1 month prior to Day 1 is allowed but not required. The dose of this therapy should remain constant throughout the study.

5. Body weight ≥45 kg and <160 kg.
6. Female patients may be of childbearing potential or of non-childbearing potential (either surgically sterilized or at least 1 year postmenopausal (confirmed by amenorrhea duration of at least 12 months and serum follicle-stimulating hormone [FSH] ≥30 mIU/mL).
   - Female patients of childbearing potential must be non-pregnant and non-lactating, and have a negative pregnancy test at Screening (serum) and at Day 1 (urine) prior to first study drug infusion.
   - Additionally, female patients of childbearing potential must be willing to use highly-effective contraception (see Section 7.1.6.4) from Screening until 90 days after the last follow-up visit.
7. Male patients, if not infertile or surgically sterilized, must agree to use highly-effective contraception (see Section 7.1.6.4) and not donate sperm from Screening until 90 days after the last follow-up visit.
8. Provision of written informed consent.
9. Be able to communicate well with the Investigator and site personnel, and agree to comply with all study procedures and requirements.

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

1. Current disease presentation consistent with Lofgren's syndrome (ie, presence of the triad of erythema nodosum, bilateral hilar lymphadenopathy on chest X-ray, and joint pain).
2. History of severe allergic or anaphylactic reactions to therapeutic proteins, or known sensitivity to ATYR1923 or to its inactive components (L-histidine, sodium chloride, sucrose, L-methionine, and polysorbate-20).
3. Treatment (within 4 months of Day 1) with biological immunomodulators such as tumor necrosis factor-alpha (TNF-α) inhibitors (eg, infliximab, adalimumab).
4. Current evidence of clinically significant cardiovascular, hepatic, renal, hematological, metabolic, or gastrointestinal disease, or has a condition that requires other treatment, may

not allow safe participation, or which in the opinion of the Investigator should preclude the patient's participation in the clinical study.

5. Clinically significant pulmonary hypertension requiring vasodilator treatment.
6. Any history of tuberculosis, or evidence of active systemic non-tuberculous fungal or mycobacterial infection within 1 year of Screening.
7. History of clinically significant cardiac, neurological, gastrointestinal, and/or renal manifestations of their sarcoidosis.
8. Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma.
9. Major surgery within 3 months prior to Day 1 or anticipated surgery during the study.
10. Any condition that necessitated hospitalization within the 3 months prior to Day 1 or is likely to require so during the study.
11. Participation in another clinical study of an investigational agent or device within 3 months (small molecules) / 6 months (biologics) or 5 half-lives (if known) of the agent, whichever is longer.
12. History of or positive results of screening for hepatitis B (hepatitis B surface antigen [HBsAg]), hepatitis C (anti-hepatitis C virus [HCV] antibodies [Ab]) or human immunodeficiency virus (HIV) (HIV Ab type 1 and 2).
13. Is an active, heavy smoker of tobacco/nicotine-containing products (defined as >20 cigarettes/day or e-cigarette equivalent).
14. Active substance abuse (drugs or alcohol) or history of substance abuse within the 12 months prior to Screening.
15. Clinically significant abnormalities in the Screening physical examination, vital signs, ECG, or clinical laboratory test results that, in the opinion of the Investigator and Medical Monitor should preclude the patient's participation in the clinical study.
16. Patient has received a live vaccination within 8 weeks before Day 1 or inoculation with a live vaccine is planned during study participation.
17. Jo-1 Ab levels >7 U/mL at Screening, or past history of Jo-1 Ab positivity.

18. Any other condition or circumstance that, in the opinion of the investigator, would be likely to prevent adequate compliance with the study protocol.
19. Significant and/or acute illness (eg, change in pulmonary status, infection requiring antibiotics) within 5 days prior to (the first) drug administration that may impact safety assessments, in the opinion of the Investigator.

Test Products, Doses, and Mode of Administration:

ATYR1923 (or matching Placebo) will be provided in vials of 25 mg/mL strength. Placebo infusion will be identical in appearance to the active drug to maintain blinding.

All investigational product will be administered via an IV infusion over a 60-minute duration.

For the preparation of the ATYR1923 dose levels the weight of the patients at Screening will be used.

Duration of Screening, Treatment and Follow-up:

The duration of patient participation is up to 28 weeks, including:

- A Screening period for up to 4 weeks in duration.
- A 20-week treatment period with six (6) study drug infusions administered every 4 weeks.
- An EOS visit, 4 weeks after last study drug infusion.

Note that patients with elevated confirmed positive Jo-1 antibody titers or who have ongoing study drug-related treatment-emergent adverse events (TEAEs) at Week 24/EOS will continue to be followed until resolution or determined by the Investigator to be stable (eg, by telephone contact or unscheduled visit).

Duration of Study: Approximately 2 years.

Study Endpoints:

Primary: **Safety**

Safety and tolerability of multiple IV doses of ATYR1923 in patients with pulmonary sarcoidosis based on the following analyses:

- Incidence of TEAEs and serious adverse events (SAEs).

Secondary: **Potential to Decrease Background Oral Corticosteroid Dose**

- Total cumulative steroid dose administered over the primary study period (Day 1 through Week 24).
- Number of patients who achieve the targeted tapered dose of prednisone 5 mg/day (or equivalent) and maintain it through Week 24.

- Exposure response analysis comparing steroid dose area under the curve (AUC) with ATYR1923 PK parameters through Week 24.

Immunogenicity

Immunogenicity of multiple IV doses of ATYR1923 in patients with pulmonary sarcoidosis based on the following endpoints:

- Incidence and titer of positive anti-drug antibody (ADA) (anti-ATYR1923) and anti-Jo-1 Ab.

Exploratory: Change from baseline in clinical measures, including:

- FVC%
- DLco
- SUV_{max} as measured by ^{18}F-FDG-PET/CT
- Health-Related Quality of Life, as assessed by the SAT, KSQ, LCQ, FAS, and SAC BDI-TDI.
- Skin lesions in patients with cutaneous involvement utilizing SPGA, body surface area assessment, and the SASI.

Change from baseline in serum and tissue biomarkers, including but not limited to:

- ACE, and sIL2R (disease serum biomarkers).
- Extracellular histidyl-tRNA synthetase (HARS), NRP2, and VEGFC (pathway serum biomarkers).
- State of immune cell anergy in peripheral blood mononuclear cells (PBMCs).
- Histopathology (skin biopsy).

P**harmacokinetics** ATYR1923 serum concentrations following multiple IV doses of ATYR1923 in all patients with pulmonary sarcoidosis.

In addition, if available, the following ATYR1923 PK parameters will be calculated:

- Time-to-steady-state PK assessment (based on comparison of mean trough levels at Weeks 4, 8, 12, 16, 20, and 24).
- Individual patient serum PK parameters: maximum concentration (C_{max}), time to maximum concentration (T_{max}), and area under the curve ($AUC_{0\text{-}wk4}$). When possible, $AUC_{wk20\text{-}wk24}$, half-life ($t_{1/2}$), clearance (CL), volume of distribution (V_z), and volume of distribution at steady state (V_{ss}) will be estimated. All parameters will be summarized by treatment group.

- Individual patient serum PK accumulation index assessment [based on ratio of 1hr (just prior to end-of-infusion [EOI]) concentrations at Week 20 versus Day 1; as well as ratio of trough concentrations at Week 24 versus Week 4).

Sample Size Considerations:

No formal sample size calculation was performed.

It is anticipated that 36 patients will be randomized in this study; the actual number of patients will depend on the number of cohorts initiated.

Statistical Methods:

Statistical analyses of all data will be primarily descriptive in nature. 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.

Schedule of Assessments:

The Schedule of Assessments is presented in Table 1.

Table 1: Schedule of Assessments

Study Period		**Treatment**													
Visit	**Screen**	**1**	**1a**	**2**	**2a**	**3**	**3a, 3b, 3c**	**4**	**4a**	**5**	**5a**	**6**	**6a**	**7**	**EOS**
Study Day	**-28 to - 1**	**D1**	**W1/ D8**	**W2/ D15**	**W3/ D22**	**W4/ D29**	**W5, 6, 7**	**W8/ D57**	**W10/ D71**	**W12/ D85**	**W14/ D99**	**W16/ D113**	**W18/ D127**	**W20/ D141**	**WK24/ D169**
Visit Window (Days)	**-**	**-**	**-**	**±2**	**±3**	**±3**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Written informed consent	X														
Telephone Contact			X		X		X		X		X		X		
Eligibility check	X	X													
Demographics	X														
Medical history	X														
Height & weight[1]	X	X				X		X		X		X		X	
Modified MRC Dyspnea Scale	X														
Physical examination[2]	X									X					X
Vital signs[3]	X	X		X		X		X		X		X		X	X
Pulse oximetry[4]	X	X				X		X		X		X		X	X
12-lead ECG[5]	X	X[5]				X		X		X[5]		X		X[5]	X
Pulmonary Function Tests[6]	X	X				X		X		X		X		X	X
DL_{CO}[7]		X								X				X	X
Pregnancy test (females only)[8]	X (serum)	X						X				X			X (serum)
Serum FSH[9]	X														
Rheumatoid factor		X													
Jo-1 antibody (serum)	X			X		X		X		X		X		X	X
ADA sampling (serum) for anti-ATYR1923 antibodies[17]	X			X		X		X		X		X		X	X
Safety laboratory testing (hematology, clinical chemistry)	X	X		X		X		X		X		X		X	X
Urinalysis[10]	X	X		X		X		X		X		X		X	X
Coagulation laboratory testing (PT, INR, PTT)	X					X		X		X		X		X	X
Serology (HBsAg, anti-HCV, and anti-HIV 1/2 tests)	X														

Study Period		**Treatment**													
Visit	**Screen**	**1**	**1a**	**2**	**2a**	**3**	**3a, 3b, 3c**	**4**	**4a**	**5**	**5a**	**6**	**6a**	**7**	**EOS**
Study Day	**-28 to - 1**	**D1**	**W1/ D8**	**W2/ D15**	**W3/ D22**	**W4/ D29**	**W5, 6, 7**	**W8/ D57**	**W10/ D71**	**W12/ D85**	**W14/ D99**	**W16/ D113**	**W18/ D127**	**W20/ D141**	**WK24/ D169**
Visit Window (Days)	**-**	**-**	**-**	**±2**	**±3**	**±3**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Serum complement, serum tryptase, and IgE[11]		X													
Plasma complement[11]		X													
^{18}F-FDG-PET/CT (optional)[12]	X											X			
Skin lesion visual assessments (if applicable)[13]	X			X		X		X		X		X		X	
Skin lesion biopsy (optional for patients at select sites)[14]	X									X					
AE assessment/Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[15]		X													
King's Sarcoidosis Questionnaire		X				X		X		X		X		X	X
Leicester Cough Questionnaire		X				X		X		X		X		X	X
Baseline/Transitional Dyspnea Indices		X				X		X		X		X		X	X
Fatigue Assessment Scale		X				X		X		X		X		X	X
Sarcoidosis Assessment Tool		X				X		X		X		X		X	X
Blood sampling (serum) for ATYR1923 PK[16]		X[16]		X		X		X		X		X		X[16]	X
PBMC collection[18]		X								X					X
Serum biomarkers[19]		X								X				X	X
Infusion site examination[20]		X				X		X		X		X		X	
Study drug administration		X				X		X		X		X		X	
OCS Taper[21]				X											

ADA = anti-drug antibodies; AE = adverse event; BMI = body mass index; D = Day; ECG = electrocardiogram; EOI = end of infusion; EOS = End-of-Study; ET= Early Termination; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRCT = high-resolution computed tomography; INR = international normalized ratio; OCS = Oral Corticosteroid; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; SOI=start of infusion; W = week(s).
On dosing days, all assessments will be performed pre-dose unless otherwise specified.

1. **Height** only at Screening.
2. P**hysical examination**. Full physical examinations are to be obtained at Screening, Week 12 and 24, abbreviated symptom-directed physical examination may be completed at other visits if needed.

3. **Vital signs** are to be obtained at every visit. On study drug administration days, vital signs are to be measured 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 are to be measured before blood sample collection. Vital signs will include blood pressure (systolic and diastolic, recorded after lying supine for 5 min), heart rate, respiratory rate. Temperature is to be obtained at Screening and on dosing days at pre-dose, 60 minutes (±15 minutes) after the SOI, and again at 4 hours (±15 minutes) after the SOI.
4. **Pulse oximetry:** continuous pulse oximetry is to be measured on dosing days from 5 minutes pre-dose until EOI, and recorded at the same time points as vital signs. On non-dosing days pulse oximetry is to be obtained with vital sign assessments.
5. **12-lead ECG** is to be obtained at Screening, within 1-hour pre-dose on dosing days. At Day 1 and Weeks 12 and 20, an ECG is to be obtained at 4 hours (±30 minutes) after SOI. The ECG is to be obtained after patients have been lying supine for 5 minutes.
6. **Pulmonary Function Testing** is to be performed using the same spirometer throughout the study. Parameters include forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio at all specified visits. A minimum of 3 efforts should be obtained that meet the acceptance criteria of the American Thoracic Society or European Respiratory Society.
7. **DL_{CO}** measurements *should* be obtained after patients have been sitting quietly for 5 minutes.
8. **Pregnancy** serum tests are to be performed on all females at Screening and at Week 24/EOS. A urine pregnancy test is to be performed at other time points indicated.
9. **FSH** only required for all female patients.
10. **Urinalysis** (semi-quantitative by dipstick): microscopy is to be performed if indicated by an abnormal and clinically significant result.
11. **Serum Complement, Tryptase/Plasma Complement, and IgE** are to be collected at Day 1 pre-dose and again if an infusion related reaction (IRR) occurs.
12. **^{18}F-FDG-PET/CT scans are optional**; patients who elect to participate agree to have imaging performed within 4 weeks prior to Day 1, and within ±5 days of Week 16 or if early termination prior to Week 16.
13. **Skin lesion evaluation:** To be completed for patients with skin lesions present. Skin lesions will be evaluated by: Skin Physician Global Assessment (SPGA), body surface Area assessment, the Sarcoidosis Activity and Severity Index (SASI).
14. **Skin lesion biopsy:** Optional for patients with skin lesions present. A non-target lesion (ie, a lesion that is not being assessed by SASI over time) is to be selected by the Investigator for biopsy during Screening and confirmed by the patient that it had been identified by his or her private dermatologist as cutaneous sarcoidosis. Skin lesion biopsy may be obtained within 4 weeks prior to Day 1 for patients who are otherwise deemed eligible for the study and within ±5 days of Week 12 or if early termination prior to Week 12.
15. **Randomization** is to be performed within 0-3 days prior to Day 1 or on the day of dosing.
16. **ATYR1923 serum PK** samples are to be collected pre-dose on dosing days. On Day 1 and Week 20 visits, PK samples are also collected post start of infusion at: 1 hr (just prior to [i.e., within 0-10 minutes] EOI), and at any single time point between 4-6 hours.
17. **ADA** samples are to be collected pre-dose when obtained on dosing days.
18. **Blood for PBMC assessments** will be collected pre-dose when obtained on dosing days.
19. **Serum for biomarkers** are to be collected pre-dose when obtained on dosing days.
20. **Infusion site examination:** the IV infusion site should be examined at 0.5 and 1.5 hours (±10 minutes) after the end of infusion.
21. **OCS Taper:** OCS taper to start at Day 15 (Week 2) and continue through Day 50 (Week 7) per the ATYR1923-C-002 OCS Taper Guideline.

LIST OF ABBREVIATIONS

Abbreviation	Definition
^{18}F-FDG-PET/CT	^{18}F-fluorodeoxyglucose positron-emission tomography combined with computed tomography
Ab	Antibody
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
APCs	Antigen-presenting cells
AST	Aspartate aminotransferase
$AUC_{0\text{-}168h}$	Area under the curve from time zero to 168 hours
$AUC_{0\text{-}336h}$	Area under the curve from time zero to 336 hours
$AUC_{0\text{-}t}$	Area under the curve from time zero to the last quantifiable time point
BSA	Body surface area
CHP	Chronic hypersensitivity pneumonitis
C_{max}	Maximum concentration
COVID-19	Coronavirus disease-2019
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed tomography
DL_{CO}	Diffusing capacity of the lungs for carbon monoxide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End-of-Study
FAS	Fatigue Assessment Scale
FEV_1	Forced expiratory volume in 1 second

Abbreviation	Definition
FSH	Follicle-stimulating hormone
FVC%	Percent predicted forced vital capacity
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
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
ILD	Interstitial lung disease
iMod	Human 59 amino acid protein
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRR	Infusion-related reaction
ITT	Intent to Treat
IV	Intravenous
IWRS	Interactive web response system
KSQ	King's Sarcoidosis Questionnaire
LCQ	Leicester Cough Questionnaire
LDH	Lactate dehydrogenase
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MRC	Medical Research Council
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP	Non-human primate
NOAEL	No-observed adverse effect level
NRP2	Neuropilin 2
OCS	Oral corticosteroids
PAD	Pharmacologically active dose
PBMC	Peripheral blood mononuclear cell
PFT	Pulmonary function test
PK	Pharmacokinetic
PM/DM-ILD	Polymyositis/dermatomyositis interstitial lung disease
QM	Once monthly
RF	Rheumatoid factor
SAC BDI-TDI	Self-administered computerized Baseline/Transitional Dyspnea Indices
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SASI	Sarcoidosis Activity and Severity Index
SAT	Sarcoidosis Assessment Tool
sIL-2R	Soluble IL-2 receptor
SOI	Start of infusion
SOP	Standard operating procedure
SPGA	Skin Physician Global Assessment
SUSAR	Serious unexpected suspected adverse reaction
SUV	Standardized uptake value
SUV_{max}	Maximum standardized uptake value

Abbreviation	**Definition**
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor-alpha
USP	United States Pharmacopeia
VEGFC	Vascular endothelial growth factor C

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1. STUDY PERSONNEL AND ADMINISTRATIVE STRUCTURE

Study Sponsor:

aTyr Pharma, Inc.
3545 John Hopkins Court, Suite #250
San Diego, CA 92121
USA

Primary Sponsor Contact:

[redacted]
ATYR1923 [redacted]
aTyr Pharma, Inc.
Telephone: [redacted]
E-mail: [redacted]

Sponsor Signatory:

[redacted]
ATYR1923 [redacted]

Medical Monitor:

[redacted]
Axiom Real-Time Metrics
Telephone: [redacted]
E-mail: [redacted]

2. INTRODUCTION

2.1. Pulmonary Sarcoidosis

Pulmonary sarcoidosis is a form of interstitial lung disease (ILD) in which immune cells play a predominant role. Chronic hypersensitivity pneumonitis (CHP), polymyositis/dermatomyositis ILD (PM/DM-ILD), and connective tissue disease associated ILD (rheumatoid arthritis ILD; systemic sclerosis-associated ILD) are examples of other immune-mediate ILDs. These lung conditions are recognized as having a measurable immune component involving both innate and adaptive immune mechanisms that contribute to pathogenesis at several cellular and non-cellular levels (Kolahian et al, 2016; Meyer et al, 2014).

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that is characterized pathologically by the presence of non-caseating granulomas (Hunninghake et al, 1999). Sarcoidosis frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. This disease affects people of all ages, but typically presents before the age of 50 years, with the incidence peaking at 20-39 years (Iannuzzi et al, 2007). The lungs are affected in more than 90% of patients with sarcoidosis (Baughman et al, 2011). Although spontaneous remissions occur, chronic or progressive disease is seen in 10–30% and the disease is fatal in 15% of patients, typically due to progressive respiratory insufficiency, central nervous system, or myocardial involvement. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved. While sarcoidosis most frequently involves the lungs and thoracic lymph nodes, up to 30 percent of patients present with extrathoracic manifestations of sarcoidosis.

In the lung, granulomas are most commonly found in the alveolar septa, the walls of bronchi, the pulmonary arteries and veins. The sarcoid granuloma is characterized by a core of monocyte-derived epithelioid histiocytes and multinucleate giant cells with interspersed CD4+ T lymphocytes (Baughman et al, 2011). A minority of cells in or near the granuloma are CD8+ lymphocytes, fibroblasts, regulatory T-cells, and B lymphocytes.

For patients with pulmonary sarcoidosis, the primary goal of treatment is to improve the patient's quality of life, while secondarily managing the inflammation that could lead to the development of more permanent fibrosis and impairment of pulmonary function. Currently, the only available therapy, H.P. Acthar® Gel, (Mallinckrodt Pharmaceuticals, 2018) for the treatment of sarcoidosis, which was approved in 1952, is not widely used by physicians due to toxicity and cost issues (Baughman et al, 2016). The consensus standard of care is oral corticosteroids (OCS) that act mainly by suppressing inflammatory genes including interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which are important to sarcoid granuloma development (Schutt et al, 2010, Judson et al, 2012). OCS therapy has been shown to stabilize or improve the

disease, although relapse commonly occurs once OCS therapy is tapered or discontinued (Iannuzzi et al, 2007). Current consensus recommends initiating treatment at a daily prednisone equivalent dose of 20 - 40 mg/day for 1 to 3 months, followed by a taper to 5 to 10 mg/day maintenance dose for 1 year (Hunninghake et al, 1999). For patients who subsequently relapse after taper or discontinuation of OCS therapy, the cycle of dosing is repeated.

Long-term corticosteroid use is associated with significant side effects, including substantial weight gain, development of insulin resistance, osteoporosis, and risk of infection. As well, a cohort of sarcoidosis experts published a consensus that a maintenance dose of greater than 10 mg/day for pulmonary sarcoidosis was to be avoided, when possible (Hunninghake et al, 1999), forming the need for steroid-sparing treatments. Yet, unremitting inflammation may progress into pulmonary fibrosis and death. Alternatives, such as immunosuppressive and cytotoxic agents (eg, methotrexate and TNF-α inhibitors) have been used; however, these therapies can also have significant side effects and toxicities. (Judson et al, 2012). Most published data on the use of these therapies is anecdotal and based on small numbers of patients and results have been variable. Infliximab (TNF-α inhibitor) was shown to improve lung function in those with chronic pulmonary sarcoidosis; however, the treatment effect was modest (Baughman et al, 2006).

Given the known toxicities of long-term corticosteroids, immunosuppressives and cytotoxic therapeutic regimens, treatment of patients with sarcoidosis is limited to those who are symptomatic and whose disease is considered ‘active’. The presence of granulomas from sarcoidosis define the disease as active (Beegle et al, 2013), and granulomatous inflammation is the major cause of fibrosis in pulmonary sarcoidosis. Studies to date have not clearly demonstrated that corticosteroids or other immuno-suppressive therapy prevents disease progression or formation of fibrosis (Baughman et al, 2011). Therefore, there exists a substantial need for safer and more effective therapies for sarcoidosis.

2.2. ATYR1923

The immunopathogenesis of sarcoidosis is not yet well understood. A leading hypothesis is that granuloma formation involves the interplay between antigen, human leukocyte antigen class II molecules, and T-cell receptors (Moller et al, 2002): a presumptive sarcoid ‘antigen’ is engulfed by circulating antigen-presenting cells (APCs; macrophages, dendritic cells) and the subsequent interplay between APCs and CD4+ T cells initiates granuloma formation (Baughman et al, 2011). T lymphocyte activation subsequently plays a crucial role in sarcoidosis pathogenesis. The T-cell response is biased towards a Th-1 phenotype, with important roles for interferon-gamma (IFN-γ) and IL-12 (Baughman et al, 2011). A variety of cytokines and chemokines have been associated with the granulomatous response in sarcoidosis, including TNF-α. Recently, TH17

effector CD4+ cells have been implicated in sarcoidosis granuloma formation (Facco et al, 2011).

ATYR1923 is a novel molecular entity that acts as an extracellular immunomodulator. ATYR1923 comprises a human 59 amino acid protein (iMod) fused to the Fc region of human immunoglobulin G1 (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 development builds upon aTyr's (Sponsor's) understanding of the biology of the extracellular activity of HARS, which we refer to as the neuropilin 2 (NRP2) pathway. Antibody blockade of the NRP2 pathway has been associated with disruption of immune, respiratory, and muscle homeostasis both in animals (Fernandez et al, 2013; Katsumata et al, 2007; Sciorati et al, 2014; Sciorati et al, 2015; Hervier et al, 2016) and in humans. In humans, the rare disease, anti-synthetase syndrome is associated with loss of immune tolerance to HARS, with resultant Jo-1 antibody (Ab) that recognizes HARS (Mathews and Berstein, 1983; Bernstein et al, 1984; Yoshida et al, 1983; Yang et al, 1984; Stone et al, 2007; Tillie-Leblond et al, 2008; Richards et al, 2009). These patients commonly manifest with myositis and ILD, and the Sponsor has determined that all Jo-1 Ab-positive patients tested have antibodies that bind to the iMod domain.

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 NRP2 was recently discovered to bind ATYR1923, and innate immune cells such as dendritic cells and macrophages are known to express NRP2 (Roy et al, 2017; Schellenburg et al, 2017), further research into the interaction between ATYR1923 and NRP2 on these cells could potentially elucidate additional mechanism through which ATYR1923 modulates the immune system. Finally, ATYR1923 has been shown to significantly reduce lung fibrosis and inflammation in bleomycin-induced animal models of ILD (Nangle et al, 2017; Ogilvie et al, 2018).

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, ATYR1923-C-001. Data from this study demonstrated single doses of ATYR1923 over the dosing range of 0.03 to 5 mg/kg to be well-tolerated in healthy volunteers 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 studies with regard to the incidence of TEAEs. Adverse reactions reported to date include headache, dizziness, and back pain.

No ATYR1923-treated subject experienced a definitive infusion-related reaction (IRR). However, the occurrence of an IRR could not be ruled out for 1 subject, who experienced mild, transient symptoms of dizziness, abdominal pain, and "feeling cold" followed by back pain after ATYR1923 infusion. No subject was positive for anti-drug antibodies (ADA) or Jo-1 Ab after ATYR1923 exposure.

ATYR1923 pharmacokinetics (PK) were dose-proportional over the range of 0.03 mg/kg to 5.0 mg/kg, and the mean half-life ($t_{1/2}$) was consistent at doses of 0.1 mg/kg and above, with mean values ranging from 167 to 242 hours (7 to 10 days), supporting the potential for convenient dosing on a monthly basis.

This study represents the first clinical investigation of ATYR1923 in patients with pulmonary sarcoidosis.

2.3. Rationale for Current Study

A large unmet need exists for a new therapy that can safely and effectively treat pulmonary sarcoidosis, a condition for which there exists a substantial need for safer and more effective therapies. The first-in-human clinical study of ATYR1923 demonstrated ATYR1923 to be well tolerated among healthy volunteers, with no significant safety concerns identified. Furthermore, PK data support convenient once monthly (QM) dosing. Accordingly, the current study is being conducted to determine the safety and tolerability, potential steroid-sparing effect, potential immunogenicity, and PK of ATYR1923 in this target patient population. The potential efficacy of ATYR1923 will also be preliminarily explored in this study.

3. STUDY OBJECTIVES

3.1. Primary

The primary objective is:

- To evaluate the safety and tolerability of multiple ascending intravenous (IV) doses of ATYR1923 in patients with pulmonary sarcoidosis.

3.2. Secondary

Secondary objectives are:

- To assess the potential steroid-sparing effect of multiple ascending doses of ATYR1923 in patients with pulmonary sarcoidosis.
- To assess the potential immunogenicity of multiple ascending IV doses of ATYR1923 in patients with pulmonary sarcoidosis.
- To characterize the PK of multiple ascending IV doses of ATYR1923 in patients with pulmonary sarcoidosis.

3.3. Exploratory

The exploratory objective is:

- To explore the preliminary efficacy of multiple ascending IV doses of ATYR1923 in patients with pulmonary sarcoidosis by evaluating changes over time in:
  - Disease activity (pulmonary parenchymal inflammation), assessed by ^{18}F-fluorodeoxyglucose positron-emission tomography combined with computed tomography (^{18}F-FDG-PET/CT) (optional).
  - Lung function, assessed by percent predicted forced vital capacity (FVC%) and diffusing capacity of the lungs for carbon monoxide (DL_{CO}).
  - Serum biomarkers, including angiotensin converting enzyme (ACE), soluble IL-2 receptor (sIL-2R), extracellular HARS, NRP2, and vascular endothelial growth factor C (VEGFC).
  - State of immune cell anergy in peripheral blood mononuclear cells (PBMCs)
  - Health-related quality of life scales, including the Sarcoidosis Assessment Tool (SAT), King's Sarcoidosis Questionnaire (KSQ), Leicester Cough Questionnaire (LCQ), Fatigue Assessment Scale (FAS), and the self-administered computerized Baseline/Transitional Dyspnea Indices (SAC BDI-TDI).
  - Skin lesions, for patients with cutaneous disease involvement at baseline, as assessed by Skin Physician Global Assessment (SPGA), body surface area (BSA)

assessment, and the Sarcoidosis Activity and Severity Index (SASI; on a target lesion), as well as serial biopsies of non-target lesion(s) (optional at select sites).

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This randomized, double-blind, placebo-controlled, study will evaluate the safety, tolerability, immunogenicity, PK, and preliminary efficacy of multiple ascending doses of IV ATYR1923 in patients with pulmonary sarcoidosis undergoing a protocol-guided OCS tapering regimen.

This study will consist of 3 staggered multiple dose cohorts, as shown in Table 2.

Table 2: Planned Dose Cohorts

Cohort	Dose (mg/kg)	# of Doses	Dosing Frequency	N	Ratio ATYR1923: Placebo
1	1.0	6	Every 4 weeks	12	2:1
2	3.0	6	Every 4 weeks	12	2:1
3	5.0	6	Every 4 weeks	12	2:1

Each eligible patient will participate in only one cohort during the study. Within each cohort, 12 patients will be randomized 2:1 (block size of 6) to ATYR1923 (N=8) or placebo (N=4). Study drug will be administered via IV infusion every 4 weeks for a total of 6 doses (20 weeks of treatment). The follow-up study visit is scheduled for 4 weeks after the last infusion. The ATYR1923 doses levels to be evaluated are 1.0 mg/kg, 3.0 mg/kg, and 5.0 mg/kg. In total, approximately 36 patients with pulmonary sarcoidosis are planned to be randomized. The dose-escalation procedure is described in Section 7.1.3.1.

Day 1 is the calendar day of first infusion.

Starting on Day 15, patients will begin a taper (reduction) in OCS (per the ATYR1923-C-002 Oral Corticosteroid Taper Guidelines) from their starting dose of 10-25 mg/day of prednisone (or equivalent) to a target dose of 5 mg/day, to be completed on or before Day 50. The OCS dose will be tapered by 5.0 mg/day every 1 to 2 weeks, depending on the starting dose. Smaller incremental titrations to the target dose of 5 mg/day by Day 50 may be implemented per Investigator judgement. Patients will be maintained at the target dose of 5.0 mg/day (or equivalent) through Week 24/End-of-Study (EOS). Optionally, further titrations in the OCS dose to below 5 mg/day may be attempted after the Week 16 visit, if determined by the Investigator to be feasible.

Patients who develop an acute worsening of symptoms or are unable to adhere to the protocol-defined OCS tapering regimen may receive ‘rescue’ treatment with higher OCS doses as clinically indicated. Upon resolution of symptoms, the Investigator may choose to reinstitute a taper back down to the target maintenance dose of 5 mg/day. Patients who require rescue treatment following 2 attempts at tapering to 5 mg/day may remain on a

higher stable dose of OCS, as determined by the Investigator. Patients who require an increase in OCS dose at any time in the study should continue to receive blinded study drug and followed through to the end of the study.

Ongoing review of blinded safety and tolerability data will be performed by the Medical Monitor and aTyr Pharma personnel.

An independent Data Safety Monitoring Board (DSMB) will perform interim reviews of unblinded safety, tolerability, and immunogenicity data from each cohort and ad hoc as per Sponsor's request if a pattern of unexpected, clinically significant trends or changes in other safety assessments is identified through blinded safety data reviews.

4.1.1. Screening Period

Patients will report to the study center for the eligibility screening (see Section 5) for inclusion and exclusion criteria) within 28 days prior to (the first) drug administration.

Patients will sign the study-specific informed consent form (ICF) prior to any study-specific screening procedures being performed. The written informed consent will be obtained for all patients, regardless of their eligibility for the study, and a copy will be provided to the patient.

Eligibility screening will consist of the assessments as presented in the Schedule of Assessments (Table 1).

4.1.2. Treatment Period

The treatment period consists of 6 administrations of study drug via IV infusion every 4 weeks for a total of 20 weeks of treatment (at Day 1 and Weeks 4, 8, 12, 16, and 20). Study drug will be administered by qualified study center personnel at scheduled study visits.

Between scheduled study visits, patients will be contacted by study center personnel via telephone at Weeks 1, 3, 5-7, 10, 14, and 18.

Assessments during the treatment period will be performed as presented in the Schedule of Assessments (Table 1).

4.1.3. Follow-up

All patients are to attend an End-of-Study (EOS) visit at Week 24, ie, 1 month after the last study drug dose. Note that patients with elevated confirmed positive Jo-1 antibody titers or who have ongoing study drug-related TEAEs at Week 24/EOS will continue to be followed until resolution or determined by the Investigator to be stable (eg, by telephone contact or unscheduled visit).

Assessments during follow-up will be performed as presented in the Schedule of Assessments (Table 1).

4.1.4. Study Completion

The study will be considered complete when the last patient completes the EOS 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 doses of ATYR1923 were found to be safe and well tolerated in a first-in-human clinical study, ATYR1923-C-001, in healthy volunteers. No significant immunogenic responses (induction of ADAs or Jo-1 Ab positivity) were observed following the administration of single doses of ATYR1923. The PK 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 $t_{1/2}$ was consistent from the 0.1 mg/kg (Cohort 2) onwards, with mean values ranging from 167 to 242 hours, supporting the potential for dosing every 4 weeks.

These data support the continued clinical evaluation of ATYR1923, including evaluations of the safety, tolerability, PK, immunogenicity, and potential efficacy of multiple doses of ATYR1923. ATYR1923 is being developed for pulmonary sarcoidosis, a condition with a significant unmet medical need. Given the significant unmet medical need for this condition, advancing safe and efficacious therapies to patients as rapidly as possible is warranted.

Several design features have been employed in the current study in an effort to minimize bias, including a double-blind design. Within each cohort, patients will be randomized, on a 2:1 basis, to receive either ATYR1923 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 E9, Statistical Principals for Clinical Trials, 1998).

The current study is specifically designed, with the inclusion of detailed safety measures, to evaluate these parameters in patients with pulmonary sarcoidosis.

Patients will be evaluated routinely during the treatment as well as 4 weeks after the last study drug dose.

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 the single-dose healthy subject study included 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. In the single-dose healthy volunteer study, neither Jo-1 Ab or ADA were detected. However, ADA have occurred infrequently in nonclinical studies with ATYR1923 in the rat and non-human primate (NHP). 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

A total of 36 patients with pulmonary sarcoidosis (24 randomized to ATYR1923 and 12 to placebo) are planned to be randomized in the study.

5.1.1. Inclusion Criteria

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

1. Male or female patients aged ≥18 to ≤75 years inclusive at time of informed consent
2. Diagnosis of pulmonary sarcoidosis for ≥6 months (cutaneous and ocular involvement allowed), defined as:
   - Histologically proven diagnosis of sarcoidosis by bronchoscopy, biopsy (any organ), or bronchioalveolar lavage.
   - Evidence of parenchymal lung involvement by historical radiological evidence (eg, computed tomography [CT], magnetic resonance imaging [MRI], ^{18}F-FDG-PET/CT or chest X-ray) or on the Screening ^{18}F-FDG PET/CT.
3. Must have symptomatic and/or active pulmonary sarcoidosis as evidence by:
   - Clinical findings of dyspnea, as indicated by a Modified Medical Research Council (MRC) Dyspnea Scale grade of at least 1; and
   - FVC% predicted ≥50%.
4. Must be receiving treatment with 10 to 25 mg/day of oral prednisone (or oral equivalent; eg, methylprednisolone), at a stable dose for ≥4 weeks prior to Day 1, and be determined by the Investigator to be capable of undergoing the protocol-specified steroid taper regimen.
   - Treatment with one oral immunomodulatory therapy (eg, methotrexate, azathioprine, hydroxychloroquine) at a stable dose for ≥1 month prior to Day 1 is allowed but not required. The dose of this therapy should remain constant throughout the study.
5. Body weight ≥45 kg and <160 kg.
6. Female patients may be of childbearing potential or of non-childbearing potential (either surgically sterilized or at least 1 year postmenopausal (confirmed by amenorrhea duration of at least 12 months and serum follicle-stimulating hormone [FSH] ≥30 mIU/mL).

- Female patients of childbearing potential must be non-pregnant and non-lactating, and have a negative pregnancy test at Screening (serum) and at Day 1 (urine) prior to first study drug infusion.
- Additionally, female patients of childbearing potential must be willing to use highly-effective contraception (see Section 7.1.6.4) from Screening until 90 days after the last follow-up visit.

7. Male patients, if not infertile or surgically sterilized, must agree to use highly-effective contraception (see Section 7.1.6.4) and not donate sperm from Screening until 90 days after the last follow-up visit.
8. Provision of written informed consent.
9. Be able to communicate well with the Investigator and site personnel, and agree to comply with all study procedures and requirements.

5.1.2. Exclusion Criteria

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

1. Current disease presentation consistent with Lofgren's syndrome (ie, presence of the triad of erythema nodosum, bilateral hilar lymphadenopathy on chest X-ray, and joint pain)
2. History of severe allergic or anaphylactic reactions to therapeutic proteins, or known sensitivity to ATYR1923 or to its inactive components (L-histidine, sodium chloride, sucrose, L-methionine, and polysorbate-20).
3. Treatment (within 4 months of Day 1) with biological immunomodulators such as TNF-α inhibitors (eg, infliximab, adalimumab).
4. Current evidence of clinically significant cardiovascular, hepatic, renal, hematological, metabolic, or gastrointestinal disease, or has a condition that requires other treatment, may not allow safe participation, or which in the opinion of the Investigator should preclude the patient's participation in the clinical study.
5. Clinically significant pulmonary hypertension requiring vasodilator treatment.
6. Any history of tuberculosis, or evidence of active systemic non-tuberculous fungal or mycobacterial infection within 1 year of Screening.
7. History of clinically significant cardiac, neurological, gastrointestinal, and/or renal manifestations of their sarcoidosis.
8. Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or effectively managed cervical carcinoma.

9. Major surgery within 3 months prior to Day 1 or anticipated surgery during the study.
10. Any condition that necessitated hospitalization within the 3 months prior to Day 1 or is likely to require so during the study.
11. Participation in another clinical study of an investigational agent or device within 3 months (small molecules) / 6 months (biologics) or 5 half-lives (if known) of the agent, whichever is longer.
12. History of or positive results of Screening for hepatitis B (hepatitis B surface antigen [HBsAg]), hepatitis C (anti-hepatitis C virus [HCV] Ab) or human immunodeficiency virus (HIV) (HIV Ab type 1 and 2).
13. Is an active, heavy smoker of tobacco/nicotine-containing products (defined as >20 cigarettes/day or e-cigarette equivalent).
14. Active substance abuse (drugs or alcohol) or history of substance abuse within the 12 months prior to Screening.
15. Clinically significant abnormalities in the Screening physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory test results that, in the opinion of the Investigator and Medical Monitor should preclude the patient's participation in the clinical study.
16. Patient has received a live vaccination within 8 weeks before Day 1 or inoculation with a live vaccine is planned during study participation.
17. Jo-1 Ab levels >7 U/mL at Screening, or past history of Jo-1 Ab positivity.
18. Any other condition or circumstance that, in the opinion of the investigator, would be likely to prevent adequate compliance with the study protocol.
19. Significant and/or acute illness (eg, change in pulmonary status, infection requiring antibiotics) within 5 days prior to (the first) drug administration that may impact safety assessments, in the opinion of the Investigator.

5.2. Source of Patients

This will be a multi-center study conducted globally. Each study center is required to obtain local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 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 assigned to a cohort 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 must provide written informed consent before the performance of any study-related procedure. Patients eligible for the study will be randomized into the study 0-3 days prior to Day 1 and will receive a total of 6 IV infusions of study drug (either ATYR1923 or placebo) administered once every 4-weeks, according to their treatment assignment on a double-blind basis. Patients will attend a post-treatment follow-up visit 4 weeks 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. Failure to attend scheduled study visits may result in discontinuation from the study.

6.3.1. Study Conduct During the COVID-19 Public Health Emergency

Note that due to the coronavirus disease-2019 (COVID-19) public health emergency, it is understood that some flexibility may be required around the timing of scheduled study visits beyond the visit windows specified in the Schedule of Assessments (Table 1). In particular, the 4-week Screening period may be extended to 6 weeks, laboratory or clinical tests may be performed locally, and telephone contacts may be utilized to follow patients with delayed or missed study visits.

Patients missing 2 consecutive study drug doses are to have study drug permanently discontinued, complete the EOS visit, and be withdrawn from the study. (Patients who withdraw from the study due to COVID-19-related issues may be replaced; see Section 6.4.3.)

Note that COVID-19 screening is not required per protocol; however, each study center is to follow standard institutional practice regarding COVID-19.

All deviations due to COVID-19 are to be documented.

6.4. Withdrawal and Replacement of Patients

6.4.1. Study Drug Discontinuation Criteria

Study drug must be discontinued if any of the following events occur:

- A serious adverse event (SAE) during or within 60 minutes of IV infusion that includes cardiac and/or respiratory observations, that has a reasonable possibility of a causal relationship with the study drug, including a severe IRR.
- Pregnancy.
- 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.
- Missing 2 consecutive study drug doses.

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 EOS visit and as clinically indicated. Patients who have skin lesions that are being followed and withdraw from the study prior to Week 12 will be asked to have a skin biopsy at the EOS Visit. If applicable, patients who withdraw from the study prior to Week 16 will be asked to have a ^{18}F-FDG-PET/CT at the EOS Visit.

Patients who decide not to receive any further study drug will be offered all follow-up safety assessments, including the EOS visit after their last infusion.

If a patient 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. 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 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.

6.4.3. 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 withdraw for reasons other than treatment-related AEs may be replaced at the discretion of the Sponsor. The decision regarding the replacement of patients will be documented.

6.5. Study Completion

A patient is considered to have completed the study if they received at least 5 of 6 scheduled study drug doses and completed 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 without prior approval from the Sponsor and regulatory authorities, 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 blinded safety and tolerability data will be performed by the Medical Monitor and aTyr Pharma personnel.

In addition, an independent DSMB will perform interim reviews of unblinded safety, tolerability, and immunogenicity data from each cohort and hoc per Sponsor request if a pattern of unexpected, clinically significant trends or changes in other safety assessments is identified through blinded safety data reviews.

The DSMB will provide its recommendation to aTyr Pharma. Such recommendation may include, but is not limited to: stopping an ongoing cohort, stopping further dose escalation, continuation of the study as planned, or continuation of the study with modifications, such as evaluation of a lower or intermediate dose in the next cohort(s) to gain more information on safety and tolerability.

7. STUDY DRUG

7.1. Study Drug Dose and Administration

7.1.1. Treatments Administered

The planned study cohorts are identified in Table 2. In all study cohorts, it is planned that study drug will be administered as an IV infusion over approximately 60 minutes every 4 weeks for a total of 6 doses (20 weeks of treatment). Within each cohort, patients will be assigned to ATYR1923 or placebo according to the computer-generated randomization list (see Section 7.1.3).

Although this is an escalating dose study, if safety or tolerability issues are experienced, or the actual ATYR1923 PK appears to be substantially different from what is predicted, a different dose or interval may be administered in the next cohort. Further, an intermediate dose may be tested to gain more information on safety, tolerability and/or PK.

For the preparation of the ATYR1923 dose levels, the patient's weight at Screening will be used.

7.1.2. Identity of Investigational Products

7.1.2.1. AYTR1923

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 will be supplied as the formulation buffer in vials that are similar in appearance to ATYR1923.

Placebo will be administered to patients by IV infusion after appropriate dilution in 0.9% sterile sodium chloride solution, USP, as outlined in the study Pharmacy Manual.

7.1.3. Method of Assigning Patients to Treatment Cohorts

After obtaining informed consent, patients will be screened according to the inclusion and exclusion criteria and will be assigned to a cohort based on their availability. Within each cohort, 12 patients will be randomized 2:1 (block size of 6) in a blinded fashion to ATYR1923 (N=8) or placebo (N=4).

7.1.3.1. Dose Escalation Procedure

Cohorts 1 through 3 will be enrolled sequentially in a staggered manner. After at least 6 patients of a given cohort have received at least 3 infusions of study drug (ATYR1923 or placebo), cumulative unblinded safety data (including but not limited to any reported AEs, ECG recordings, clinical laboratory tests, and vital signs) will be reviewed by the DSMB. Enrollment in the next scheduled cohort may commence after this review is completed, dose escalation is approved, and the remaining 6 patients have been randomized in the previous cohort. Dose escalation will continue in this manner until the highest planned dose level of ATYR1923 is reached, or the criteria for pausing enrollment have been met (see Section 7.1.3.2).

7.1.3.2. 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 an ongoing cohort, stopping further dose escalation, continuing the study as planned, or continuing the study with modifications, such as evaluation of a lower or intermediate dose in the next cohort(s) to gain more information on safety and tolerability.

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

7.1.4. Selection of Doses in the Study

7.1.4.1. First-in-Human Study ATYR1923-C-001

The first in human study ATYR1923-C-001 evaluated single ascending dose administration of ATYR1923 at doses of 0.03, 0.1, 0.3, 1, 3.0 and 5.0 mg/kg.

The ATYR1923 starting dose of 0.03 mg/kg was based on: 1) the no-observed adverse effect level (NOAEL) from non-clinical Good Laboratory Practice toxicity studies;

2) estimation of the human minimum pharmacologically active dose (PAD) level range (0.035 to 0.1 mg/kg) based on total body weight; and 3) estimation of human PAD based on predicted ATYR1923 human serum PK parameters, determined from single species (NHP) allometric scaling to humans. These approaches supported a human starting dose level for ATYR1923 of 0.03 mg/kg, which was just below the lower end of the human PAD calculation range (0.035–1.0 mg/kg) and well below the maximum recommended starting dose (0.97 mg/kg). The highest single dose (5.0 mg/kg) planned in the first-in-human Phase 1 study was anticipated to produce mean serum exposure levels that remained at least 2-fold below those seen in animal toxicity testing at the NOAEL.

7.1.4.2. Current Study in Patients with Pulmonary Sarcoidosis

The proposed doses in the current study in patients with pulmonary sarcoidosis are 1.0 mg/kg (Cohort 1), 3.0 mg/kg (Cohort 2), and 5.0 mg/kg (Cohort 3). Cohorts will be enrolled sequentially in a staggered manner.

Selection of the proposed doses is primarily informed by clinical and pharmacological findings from ATYR1923-C-001, in which single doses of ATYR1923 were well tolerated across the broad dose range from 0.03 up to 5.0 mg/kg, with no clear dose-relationship with regard to the incidence of TEAEs, or changes in clinical laboratory parameters or other safety measures. No SAEs or severe AEs were reported at any dose, indicating that the starting dose of 1.0 mg/kg dose in this study should be acceptable.

Repeat administration of ATYR1923 once monthly is expected to result in little or no accumulation of peak (ie, maximum concentration [C_{max}]) and total (ie, area under the curve [AUC]) serum exposure measures at steady-state when compared to single dosing. For example, C_{max} and area under the curve from time zero to 168 hours ($AUC_{[0\text{-}168h]}$) after the 6th monthly dose of ATYR1923 at 5 mg/kg is predicted to be 109,618 ng/mL and 3,577,275 ng·h/mL, respectively; estimates that are highly similar to the values observed after a single dose of ATYR1923 at 5 mg/kg in ATYR1923-C-001 (109,250 ng/mL and 3,417,001 ng·h/mL, respectively).

In a Good Laboratory Practice-compliant 6-month duration toxicology study in NHPs, the NOAEL was 60 mg/kg by IV injection once weekly, the highest dose administered. The mean serum exposures ($AUC_{[0\text{-}168h]}$) measured at the NOAEL in this study ranged from 27,900,000 ng·h/mL (Day 1) to 44,400,000 ng·h/mL (Day 176). Comparison of the mean serum exposures observed in NHPs with those predicted in subjects after the 6th monthly dose of ATYR1923 at the 5 mg/kg dose (3,577,275 ng·h/mL) estimates a safety margin of 8-12-fold. Safety margins based on comparison of mean maximal concentrations (mean C_0 ranged from 1,880,000-2,080,000 ng/mL in NHPs versus the mean predicted C_{max} of 109,618 ng/mL in humans) are higher at 17-19-fold. Therefore, repeat-dose administration of ATYR1923 to patients over a 6-month duration at doses up to 5 mg/kg is expected to produce mean serum exposures that remain well below those seen in animal toxicity testing for up to 6 months.

7.1.5. Blinding

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

- The infusion solution containing 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.
- PK results for the interim analyses will be presented in a blinded fashion.

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:

- Immunomodulatory agents, such as TNF-α inhibitors (eg, infliximab, adalimumab), are prohibited from 4 months of Day 1 and through the duration of study drug treatment.
- Live vaccination within 8 weeks before Day 1 and during study participation is prohibited.
- 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.
- Major surgeries are prohibited from 3 months before the first study drug dose through the duration of study drug treatment.

- Heavy smoking/inhalation of tobacco/nicotine-containing products >20 cigarettes/day or e-cigarette equivalent.
- Topical treatment of any lesion identified by the Investigator for cutaneous assessments (eg, biopsy).

All other concomitant medications and procedures are allowed.

Concomitant medications are to be recorded in the source documents and in the eCRF.

7.1.6.2. Oral Corticosteroid Taper

Starting on Day 15, patients will begin a taper (reduction) in OCS (per the ATYR1923-C-002 Oral Corticosteroid Taper Guidelines) from their starting dose of 10-25 mg/day of prednisone (or equivalent) to a target dose of 5 mg/day, to be completed on or before Day 50. The OCS dose will be tapered by 5.0 mg/day every 1 to 2 weeks, depending on the starting dose. Smaller incremental titrations to the target dose of 5 mg /day by Day 50 may be implemented per Investigator judgement. Patients will be maintained at the target dose of 5.0 mg/day (or equivalent) through Week 24/EOS. Optionally, further titrations in the OCS dose to below 5 mg/day may be attempted after the Week 16 visit, if determined by the Investigator to be feasible.

Patient will document OCS doses in a diary, which will be reviewed at relevant scheduled telephone contacts and study visits.

7.1.6.3. Rescue Treatment with Oral Corticosteroids

Patients who develop an acute worsening of symptoms or are unable to adhere to the protocol-defined OCS tapering regimen may receive 'rescue' treatment with higher OCS doses as clinically indicated.

The following criteria should be met prior to providing rescue OCS treatment:

1a) Worsening cough, documented by a decrease of ≥1 point on the LCQ,

OR

1b) Worsening dyspnea, documented by an increase of ≥1 point on the TDI,

AND

2) The Investigator's clinical judgement that rescue therapy is warranted.

Rescue therapy is not mandated in the event of worsening cough or worsening dyspnea if the Investigator determines that an increase in steroid dose is not clinically indicated.

Upon resolution of symptoms, the Investigator may choose to reinstitute a taper back down to the target maintenance dose of 5 mg/day.

Patients who require rescue treatment following 2 attempts at tapering to 5 mg/day may remain on a higher stable dose of OCS as determined by the Investigator.

Patients who require an increase in OCS dose at any time in the study should continue to receive blinded study drug and followed through to the end of the study.

Patient will document OCS doses in a diary, which will be reviewed at relevant scheduled telephone contacts and study visits.

7.1.6.4. Contraception

For this study, male patients will be considered to be of non-childbearing potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female patients will be considered of non-childbearing potential if they are either surgically sterilized (eg, hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion) or at least 1 year postmenopausal (confirmed by amenorrhea duration of at least 12 months and serum FSH ≥30 mIU/mL).

Female patients of childbearing potential must be non-pregnant and non-lactating, and have a negative pregnancy test at Screening (serum) and at Day 1 (urine) prior to first study drug infusion. A urine pregnancy tests must be repeated at Weeks 8 and 16 and a serum pregnancy test must be repeated at Week 24.

Female and male patients of childbearing potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 90 days after the last dose of study drug by complying with one of the following:

- Practice abstinence[1] from heterosexual activity. (If a patient who was initially abstinent decides to be sexually active during study participation, the patient must agree to use highly-effective contraception, as outlined below.)

  OR

- Use (or have their partner use) highly-effective contraception during heterosexual activity. Examples of highly-effective methods of contraception include:

  Single method (one of the following is acceptable):

  - Intrauterine device.
  - Vasectomy of a female patient's exclusive male partner.

[1] Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IRB/IEC. **Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.**

- Contraceptive rod implanted into the skin.

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide).
- Cervical cap with spermicide (nulliparous women only).
- Contraceptive sponge (nulliparous women only).
- Male condom or female condom (cannot be used together).
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

Refer to the Clinical Trials Facilitation Group guidelines (available at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf) for additional details regarding highly effective birth control methods (i.e., methods that can achieve a failure rate of less than 1% per year when used consistently and correctly).

If a highly effective contraceptive method is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in that location.

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 8.2.5).

The exact times of study drug infusion start and completion and number of milligrams and total volume administered will be recorded in the eCRF.

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 must provide written 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

A complete medical history, including history of pulmonary sarcoidosis and prior treatments thereof, is to be documented during Screening.

8.2.4. Serology

A blood sample for serology, including HIV1 and 2, HBsAg, and anti-HCV, is to be collected during Screening. Patients with positive results are not eligible for study participation.

Rheumatoid Factor (RF) will also be tested at Day 1. ATYR1923 is an FC-fusion protein and as such, the presence and binding of RF to the FC region of ATYR1923 could confound the detection of ADA. Rheumatoid factor positivity status will be used to facilitate the interpretation of ADA assay results and in the modification of the ADA assay to detect only antibodies directed against the therapeutic part of the molecule. RF positivity will not exclude the patient from the study.

8.2.4.1. Modified MRC Dyspnea Scale

The Modified MRC Dyspnea Scale is a five-level rating scale based on the patient's perception of dyspnea in daily activities, ranging from none (Grade 0) to very severe dyspnea (Grade 4). The score is the number that best fits the patient's level of activity. All the questions relate to everyday activities and are generally easily understood by patients. A score can usually be obtained in a few seconds.

The Modified MRC Dyspnea Scale is to be administered during Screening.

8.2.5. Quality of Life Measures

All quality of life assessments are to be performed before other study procedures at each designated visit and are to be completed in the same order at each designated visit.

8.2.5.1. Sarcoidosis Assessment Tool

The SAT is a sarcoidosis-specific patient-reported outcome developed for use in sarcoidosis clinical studies to measure the patient's assessment of impact of disease and response to therapy. The SAT requires approximately 5–10 minutes for completion (Judson et al, 2015).

The SAT Tool is to be administered at the time points designated in Table 1.

8.2.5.2. The Self-Administered Computerized Baseline and Transitional Dyspnea Indices (SAC BDI-TDI)

The BDI measures the severity of dyspnea at the baseline (or the beginning of a clinical study), and the TDI measures changes from this baseline (transition period) at subsequent visits. The BDI and TDI each contain 24 items, with items on the BDI rated in 5 grades from 0 (very severe) to 4 (no impairment), and items on the TDI rated by 13 grades ranging from -6 (major deterioration) to +6 (major improvement). The lower the score on the BDI, the worse the severity of dyspnea at baseline and the lower the score on the TDI, the more deterioration in the severity of dyspnea. The minimal clinically important difference of the TDI is a total score of 1 (Witek and Mahler, 2003). The SAC BDI-TDI takes approximately 5-10 minutes to complete.

The SAC BDI-TDI indices are to be administered at the time points designated in Table 1.

8.2.5.3. King's Sarcoidosis Questionnaire

The KSQ is an online 29-item questionnaire to be completed by sarcoidosis patients (Patel et al. 2012). The KSQ is split into 5 sections; general health status, lungs, medication, skin, and eyes. Results are given as a number between 1-100 with higher numbers indicating better health. The questionnaire takes approximately 10 minutes to complete.

The KSQ is to be administered at the time points designated in Table 1.

8.2.5.4. Leicester Cough Questionnaire

The LCQ is a 19-item self-completed quality of life measure of chronic cough which is responsive to change (Birring et al, 2003). Items on the scale are divided into 3 domains, physical, psychological, and social. Items are scored on a 7-point Likert scale. A total score (range 3 to 21) is also calculated by adding the domain scores together, with higher scores indicating better quality of life. The questionnaire takes 5 to 10 minutes to

complete (Ward, 2016). The minimal clinically important difference (MCID) for chronic cough is 1.3 (Raj et al, 2009).

The LCQ is to be administered at the time points designated in Table 1.

8.2.5.5. Fatigue Assessment Scale

The FAS contains 10 specific fatigue questions that have been validated in sarcoidosis patients (De Vries et al, 2004). On each question, one of 5 answer categories can be chosen, from never to always: 1=never; 2=sometimes (about monthly or less); 3=regularly (about a few times a month); 4=often (about weekly); 5=always (about every day). An answer to each question has to be given, even if the person does not have any complaints at the moment. Scores on questions 4 and 10 should be recoded (1=5, 2=4, 3=3, 4=2, 5=1). Subsequently, the total FAS score can be calculated by summing the scores on all questions (the recoded scores for question 4 and 10). The sum of questions 3 and 6–9 indicates mental fatigue, and the sum of the questions 1, 2, 4, 5 and 10 indicates physical fatigue. The minimal score is 10, and the maximal score is 50. Scores of ≥22 are considered to represent substantial fatigue. A change in the FAS score of 4 points is considered to be the MCID (de Kleijn et al, 2011). The FAS takes approximately 5-10 minutes to complete.

The Fatigue Assessment Scale is to be administered at the time points designated in Table 1.

8.3. 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. The blood samples will be taken via an indwelling IV catheter or by direct venipuncture into plain serum tubes. 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.

8.4. Pharmacodynamic/Exploratory Measurements and Variables

8.4.1. Blood for Peripheral Blood Mononuclear Cells and Serum Biomarkers

Blood samples for the analysis of PBMCs and biomarkers in serum will be taken at the time points designated in Table 1. The blood samples will be taken via an indwelling IV catheter in tubes containing anticoagulants or by direct venipuncture into plain serum tubes. The exact times of blood sampling will be recorded in the eCRF.

The state of immune cell anergy in PBMCs will be measured by flow cytometry and cytokine secretion, at baseline and after activation with T-cell receptor-dependent and -independent stimuli. Immunophenotyping may also be performed.

Serum biomarkers to be measured will include, but will not be limited to, ACE, sIL-2R, extracellular HARS, NRP2, and VEGFC.

Details on sample collection, handling, storage and shipping of blood samples for analysis will be described in the study Laboratory Manual prepared by Sponsor and study center.

8.4.2. Pulmonary Function Tests

Pulmonary function tests (PFTs), including FVC, forced expiratory volume in 1 second (FEV_1), and FEV_1/FVC ratio, are to be determined by spirometry at the time points designated in Table 1.

Spirometry testing will be performed according to the American Thoracic Society/European Respiratory Society guidelines (Miller et al, 2005). The spirometry equipment will be supplied to each site for the study. The same spirometry equipment should be used for all assessments performed for a patient. A limited number of staff, as designated by the investigator, will evaluate all patients at all visits throughout the entire trial. Where possible the same technician should perform all maneuvers for an individual patient. All staff conducting the spirometry tests must have received appropriate training which must be documented. Information on the procedure can be found in the Instructions for Use Manual.

Spirometry ideally is to be performed with the patient in a seated position for at least 2 minutes and wearing nose-clips; the patient is to remain seated throughout the test procedure. It is recommended that the test be performed at least 1 hour after a light meal, with the patient having refrained from recent exercise. Spirometry is to be performed in the same manner across all assessment time points.

If the patient cannot tolerate nose-clips and/or cannot perform the maneuver in a seated position, then spirometry may be performed without nose-clips and/or in a standing position; however, all subsequent assessments are to be performed in the same manner.

8.4.3. Diffusion Capacity

DL_{CO} is to be measured using the single-breath technique at the time points designated in Table 1. DL_{CO} measurements should be obtained after patients have been sitting quietly for 5 minutes.

DL_{CO} is to be corrected for hemoglobin.

8.4.4. Cutaneous Disease Assessment (for Patients with Cutaneous Disease)

For patients with cutaneous disease at baseline, cutaneous disease will be assessed by the Investigator using the SPGA, BSA assessment, and SASI.

The patient's overall skin health will be assessed by the Investigator during Screening and at the time points designated in Table 1 using the SPGA, a visual analog scale ranging from 0 (perfect health) to 10 (worst skin condition imaginable).

The handprint method, with 1 handprint equaling ~1% BSA, will be used to determine the percentage of the body surface is affected by cutaneous disease.

The SASI is an instrument that will be used to evaluate a lesion prospectively identified as the 'target' lesion, located anywhere on the body. The Investigator will score the extent of erythema and induration of this lesion, each on a scale ranging from 0 (none) to 4 (very severe) (Baughman et al, 2012; Drake et al, 2013; Judson et al, 2014).

Topical treatment of target lesion selected for the SASI assessment should be avoided.

8.4.5. Cutaneous Lesion Biopsy (Optional at Selected Sites for Patients with Cutaneous Disease)

For patients with cutaneous disease, a non-target lesion (ie, a lesion that is not being assessed by the SASI over time) is to be selected during Screening by the Investigator and confirmed by the patient that it had been identified by his or her private dermatologist as cutaneous sarcoidosis. The lesion is to be biopsied (skin punch) during Screening and again at Week 12 (±5 days), or at early termination if occurring prior to Week 12. Skin punch biopsy is to be performed according to standard institutional practice with regard to antiseptic preparation technique and local anesthesia.

8.4.6. Whole Body ^{18}F-FDG-PET/CT

In this study, patients who elect to do so will undergo whole-body head to mid-thigh ^{18}F-FDG imaging on a PET/CT scanner with a reconstructed resolution of ≤5 mm. Whole body ^{18}F-FDG is to be performed within 4 weeks prior to Day 1, within ±5 days of Week 16, or at early termination if occurring prior to Week 16. Patients with glucose levels above 11 mmol/L (200 mg/dL) should have their scan delayed or be rescheduled as appropriate. The blood glucose level measured prior to the radiotracer administration should be recorded in an image transmittal form. Patients are to fast for a minimum of 4 hours prior to the injection of ^{18}F-FDG. During the uptake phase, patients are to rest quietly and to refrain from talking, walking, and any other muscular activity to prevent non-specific FDG uptake in the skeletal muscles. The radiotracer will be administered through an IV line, after which the patient will be positioned comfortably in a supine position to rest for 60 to 90 minutes while the radiotracer distributes through the body.

Patients will be asked to void their bladder prior to the scanning procedure.

A whole body low-dose attenuation correction CT will be acquired with a whole body effective dose of 1.5 mSv. The maximum injected radioactivity dose of 555 MBq of ^{18}F-FDG will result in a maximum whole body effective dose per PET/CT timepoint of ≤8.5 mSv, dependent upon patient habitus and calculated injected activity. As a weight-

based dose approach is allowed and is dependent upon subject weight, it is possible that in large or obese patients, a higher ^{18}F-FDG activity may be required to ensure sufficient imaging quality; however in such cases, the injected activity will not exceed 555 MBq.

The baseline and follow-up ^{18}F-FDG uptake PET scan will be assessed centrally by a qualified nuclear medicine physician visually and quantitatively using standardized uptake values (SUVs) and results will be compared with baseline scan. SUV is taken as an index of disease activity. Total injected activity and body weight will be recorded and used to compute SUV values. PET response will be determined by the nuclear medicine physician according to the European Organization for Research and Treatment of Cancer criteria.

The total dose for all PET scanning in this protocol will be maximally 17 mSv in larger or obese patients who have received a higher ^{18}F-FDG injected dose.

Detailed information will be provided in a separate ^{18}F-FDG-PET/CT Imaging Manual.

8.5. Safety and Tolerability Measurements

Safety and tolerability assessments will consist of physical examinations, vital signs and temperature, 12-lead ECGs, pulse oximetry, weight, immunogenicity, AEs, and clinical laboratory tests. Concomitant medications also will be documented. Assessments will be performed in accordance with the Schedule of Assessments.

8.5.1. Physical Examination and Infusion Site Examination

A complete physical examination is to be performed during Screening and at Week 12 and Week 24/EOS. The complete physical examination is to include measurement of height during Screening.

Complete physical examinations also will include a review of the following body systems:

- General appearance.
- Head, eyes, ears, nose, and throat.
- Respiratory.
- Cardiovascular.
- Abdomen.
- Neurologic.
- Extremities.
- Dermatologic.

Abbreviated symptom-directed physical examinations are to be performed at the other study visits, as indicated.

The findings of each examination are to be documented in the eCRF.

The IV infusion site will be examined at 0.5 and 1.5 hours (+10 minutes) after the end of each study drug infusion. Any clinically significant findings will be recorded as AEs.

8.5.2. Vital Signs and Temperature

Vital signs, including blood pressure, heart rate, and respiration rate, are to be measured at the time points designated in Table 1.

At each clinic visit, vital signs are to be measured before blood sample collection that day. Heart rate and blood pressure determinations will be measured after the patient has been lying supine for at least 5 minutes.

On study drug administration days, vital signs are to be measured 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 are to be measured before blood sample collection.

Temperature is to be measured at the time points designated in Table 1. On study drug administration days, temperature is to be measured pre-dose, 60 minutes (±15 minutes) after the SOI, and again at 4 hours (±15 minutes) after the SOI. Temperature is to be measured at the same time as vital signs.

8.5.3. Electrocardiogram

A 12-lead ECG is to be performed at the time points designated in Table 1 after the patient has been lying supine for at least 5 minutes. On all study drug dosing days, the ECG is to be performed within 1 hour pre-dose. At Day 1 and Weeks 12 and 20, an ECG also is to be performed at 4 hours (±30 minutes) after the SOI.

The ECG will be recorded using an ECG machine equipped with computer based interval measurements The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTc-interval (Fridericia's) and the interpretation of the ECG profile by the Investigator.

8.5.4. Pulse Oximetry

Continuous pulse oximetry is to be performed at the time points designated in Table 1. On study drug administration days, continuous pulse oximetry is to be performed from 5 minutes pre-dose until the end of study drug infusion, and also obtained and recorded at the same time points as vital signs. On non-study drug administration days, pulse oximetry is to be obtained with vital sign assessments (see Section 8.5.2).

8.5.5. Height and Weight

Height will be measured at Screening only. Weight is to be measured at the time points designated in Table 1.

The patient's Screening weight is to be used to calculate the study drug dose. If the patient has experienced a notable change in weight (±10%), the patient's study drug dose

will be recalculated. Any change in study drug dose is to be documented in the source documents and in the eCRF.

8.5.6. Immunogenicity Measurements

Blood samples for determination of Jo-1 Ab levels in serum will be collected at the time points designated in Table 1. Those with a level considered equivocal or positive (ie, >7 U/mL) for the assay will not receive study drug. Any patients who develops positive Jo-1 antibodies will also be monitored clinically for signs/symptoms of anti-synthetase syndrome.

In addition, blood samples for determination of ADAs against ATYR1923 in serum will be collected at the time points designated in Table 1. ADA blood samples collected during Screening from patients who subsequently are determined to be screen failures will be used towards additional modification and validation of the ADA assay.

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

8.5.7. Adverse Events

AEs will be recorded from the time of written informed consent through the last visit for a patient. Any clinically significant observations in results of clinical laboratory, 12-lead ECGs, 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.

At study visits, patients will be asked non-leading questions to determine the occurrence of AEs. Patients will be asked in general terms about any AEs at regular intervals during the study. In addition, all AEs reported 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 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.

8.5.8. Concomitant Medications

All medications and supplements the patient receives during the course of the study are to be documented in the source documents and in the eCRF.

8.5.9. Safety Laboratory Tests

Blood and urine samples for clinical laboratory assessments will be collected according to the Laboratory Manual and study center standard operating procedures (SOPs).

The following parameters will be measured:

- Clinical chemistry (serum quantitatively):
  - Total bilirubin, alkaline phosphatase, gamma glutamyl transferase (gamma-GT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase, albumin, creatinine, blood urea nitrogen, total protein, glucose, inorganic phosphate, sodium, potassium, calcium and chloride, complete lipid panel.
- 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

- Serum Complement, Tryptase/Plasma Complement and immunoglobulin E (IgE):
  - Blood samples for serum complement, tryptase/plasma complement and IgE are to be collected at Day 1. Such test are to be repeated if a patient experiences an IRR (see Section 9.9).

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).

The procedures for the collection, handling, and shipping of laboratory samples are specified in the Laboratory Manual provided to the study site.

8.5.10. Pregnancy Testing and Follicle Stimulating Hormone

FSH will be measured in all female patients during Screening. Female patients of childbearing potential must have a serum pregnancy test performed during Screening and a urine pregnancy test performed at Day 1 prior to first study drug infusion. Any patient with a positive pregnancy test result is not eligible for study participation.

Additional pregnancy testing is to be performed during the study at the time points indicated in Table 1. Pregnancy test results are to be obtained and confirmed to be negative prior to randomization and study drug infusions.

All serum samples will be analyzed by the central laboratory, and urine samples will be analyzed locally. Any patient determined to be pregnant during study participation must have study drug permanently discontinued immediately (see Section 6.4.1 and Section 9.8).

8.5.10.1. Total of Blood Volume

The total volume of blood to be collected over the duration of the study is approximately 450 mL (ranging from 30 mL to 75 mL per visit).

8.5.11. Appropriateness of Measurements

The assessments, which will be made in this study are standard, and generally recognized as reliable, accurate and relevant. Assessments will be performed according to the study site.

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
- is life-threatening (ie, places the patient at immediate risk of death)
- requires in-patient hospitalization (overnight stay) or prolongation of existing hospitalization
- 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.

A hospitalization meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight (≥24 hours) stay in a health care facility. Any AE that does not meet one of the definitions of serious (ie, emergency room visit, out-patient surgery, or requires urgent investigation) may be considered by the Investigator to meet the "important medical event" criterion for classification as an SAE.

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 written informed consent 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 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.

Serious/Non-Serious

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

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 (i.e., dechallenge);

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

The relationship between the study drug and the AE will be described using one of the following categories Table 3.

Table 3: 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

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 are to be rated by the Investigator according to the categories in Table 4.

Table 4: 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

Outcome

The outcome of each AE will be described using the categories in Table 5.

Table 5: 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 (e.g., 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

Study Drug Action

For each AE, the Investigator will indicate the action taken regarding the administration of study drug per the categories in Table 6.

Table 6: 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, ie, one or more doses were not administered, but drug was not stopped permanently
Dose Decreased	Study drug regimen was modified by subtraction, ie, by decreasing the frequency, strength or amount
Dose Increased	Study drug regimen was modified by addition, ie, by increasing the frequency, strength or amount
None	No change in the administration of study drug

9.3. Recording Adverse Events

All AEs occurring from the time of written informed consent 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 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 ID 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/IEC 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/IEC 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/IEC within 7 calendar days, and additional information within an additional 8 calendar days. The Sponsor or Sponsor¹s designee is required to submit any other SUSAR to the National Regulatory Authority(ies)/IRB/IEC 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/IEC 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/IEC'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 (e.g., COVID-19 public health 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. Deviations specifically due to COVID-19 are to be documented as such.

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. Subsequent dosing should continue to occur in a facility where the patient can be monitored closely. The Investigator, in consultation with the Medical Monitor, may opt to adjust the infusion duration and/or administer pre-medication (antihistamines, non-steroidal anti-inflammatories and anti-emetics) if clinically indicated, although this is not mandatory.

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.

Once the patient is stabilized, additional blood samples are to be collected and procedures performed as outlined below:

- Vital signs, pulse oximetry, infusion site examination, 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). Vital signs are to be monitored as medically indicated and pulse oximetry is to be monitored continuously for at least 2 hours or until the patient has recovered, whichever is longer. ECGs should be repeated as medically indicated.

Once medical treatment of the IRR has begun, blood samples are to be obtained for assessment of:

- Plasma complement factors (C3a, C4a, C5a, Bb, SC5b-9).
- Serum complement (CH50, C3, and C4) and tryptase.
- ATYR1923 serum concentrations.
- Jo-1 and ADA.

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

- Samples for assessment of:
  - Complete safety laboratory panel, including urine analysis and urine microscopy.
  - IgE.
  - Plasma complement factors (C3a, C4a, C5a, Bb, SC5b-9).
  - Serum complement (CH50, C3, and C4) and serum tryptase.

- Serum biomarkers/cytokines.

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 Intent to Treat (ITT) Set will comprise all randomized patients and will be based on the randomized cohort and treatment, regardless of which treatment the patient actually received.

10.1.1.2. Safety Set

The Safety Set will comprise all patients who receive any amount of study drug and will be based on the actual treatment received, if this differs from that to which the patient was randomized.

10.1.1.3. Pharmacokinetic Concentration Set

The PK Concentration Set will comprise all patients who receive any amount of study drug, who have at least 1 quantifiable PK concentration and will be based on the actual treatment received, if this differs from that to which the patient was randomized to. A quantifiable PK concentration will be determined at the discretion of the pharmacokineticist. Patients who receive only placebo will be excluded from the PK Concentration Set.

10.1.1.4. Pharmacokinetic Parameters Set

The PK Parameters Set will comprise all patients who receive any amount of study drug, who have at least 1 evaluable PK parameter and will be based on the actual treatment received, if this differs from that to which the patient was randomized. An evaluable PK profile allows the determination of 1 or more PK parameters and will be determined at the discretion of the pharmacokineticist. Patients with dosing deviations that could potentially affect the PK profile will be excluded from the PK Parameters Set, at the discretion of the pharmacokineticist. Patients who receive only placebo will be excluded from the PK Parameters Set.

10.1.1.5. Efficacy Set

The Efficacy Set will comprise all randomized patients who receive any amount of study drug and who have at least 1 post-baseline efficacy assessment and will be based on the actual treatment received, if this differs from that to which the patient was randomized.

10.1.1.6. Oral Corticosteroid Evaluation

The oral corticosteroid evaluation 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. Further details on how data from patients who discontinued prematurely will be handled and the types of exposure response analyses that will be performed will be provided in the Statistical Analysis Plan (SAP).

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

A 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 CSR of 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. Vital Signs, Pulse Oximetry and Electrocardiograms

Vital signs, pulse oximetry and ECG parameters will be listed and they will be presented descriptively, where applicable.

10.1.2.3.4. 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 Exploratory Variables

Exploratory variables will be listed and presented descriptively, where applicable.

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/IEC 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

Written 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 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 documents. Prior to submission of the study center-specific ICF form to the IRB/IEC, these documents must be reviewed and approved by the Sponsor or designee. Any changes requested by the IRB/IEC must also be approved by the Sponsor or designee. The final IRB/IEC-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 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 understands the commitments of participating in the study, the patient will be asked to sign and date the ICF, as appropriate.

A copy of the fully signed and dated ICF will be given to the patient. The original will be maintained in the patient's medical record at the study center. All active patients will sign an updated ICF if revisions are made to the ICF during the course of the study.

11.3. Institutional Review Board/Independent Ethics Committee

Federal regulations and ICH require that approval be obtained from an IRB/IEC 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/IEC.

All IRB/IEC approvals must be dated and signed by the IRB/IEC Chairperson or designee and must identify the IRB/IEC 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/IEC 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/IEC. 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/IEC 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/IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB/IEC 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/IEC 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 representative will conduct telephone or a study visit to verify the qualifications of each Investigator, review/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 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 conduct remote or study visits to verify the qualifications of each Investigator, review/inspect 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 conduct remote monitoring or study visits to 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.

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