aTyr Pharma, Inc.

An Open-Label Extension Study to Evaluate the Long-Term Safety, Tolerability, and Biological Activity of ATYR1940 in Patients with Limb Girdle and Fascioscapulohumeral Muscular Dystrophy

Protocol Number: ATYR1940-C-006

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 [redacted] aTyr Pharma, Inc. Telephone: [redacted] E-mail: [redacted] Sponsor Signatory [redacted] aTyr Pharma, Inc. Mobile Telephone: [redacted]
IND Number:	122045
EudraCT Number:	2016-000624-25
Document Date (Version):	22 March 2016 (Version 1.0; Original)

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)/Ethics Committee (EC). No changes will be made to the study protocol without the prior written approval of aTyr and the IRB/EC, 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: An Open-Label Extension Study to Evaluate the Long-Term Safety, Tolerability, and Biological Activity of ATYR1940 in Patients with Limb Girdle and Fascioscapulohumeral Muscular Dystrophy

Protocol Number: ATYR1940-C-006

Study Phase: 1b/2a

Investigators / Study Centers: This is a multi-national, multi-center study being conducted at centers in the United States (US) and Europe who participated in the Study ATYR1940-C-003 (Stage 1 only) or ATYR1940-C-004 (i.e., the parent studies).

Study Objectives: The objectives of this study are to:

- Evaluate the safety, tolerability, and immunogenicity of long-term treatment with intravenous (IV) ATYR1940 in patients with limb girdle muscular dystrophy 2B (LGMD2B) or fascioscapulohumeral muscular dystrophy (FSHD) previously enrolled in clinical study ATYR1940-C-003 (Stage 1 only) or ATYR-1940-C-004.
- Explore the biological and pharmacodynamic (PD) activity of ATYR1940 in patients with LGMD2B and FSHD, based on changes in:
  - Serum-based muscle biomarkers.
  - Inflammatory immune state in peripheral blood.
  - Muscle disease and muscle disease burden, based on skeletal muscle magnetic resonance imaging (MRI).
  - Skeletal muscle strength.
  - Upper and lower extremity muscle function.
  - Quality of life measures.

Study Design: Study ATYR1940-C-006 is a multi-national, multi-center, open-label extension study designed to evaluate the long-term safety, effects on muscle, and PD of ATYR1940 in patients with LGMD2B or FSHD previously treated in the Protocol ATYR1940-C-003 (Stage 1 only) or ATYR1940-C-004 (i.e., the parent studies). This study will be conducted at the same study centers at which patients were enrolled in the parent studies.

Patients who completed the treatment period in the parent study; in the Investigator's opinion, demonstrated acceptable tolerability of ATYR1940, are considered by the Investigator to be compliant with ATYR1940 and the study procedures, and do not meet any criterion

	for ATYR1940 discontinuation are eligible for participation in the current study, contingent upon Investigator and patient agreement to continue ATYR1940 treatment. Ideally, when a patient transfers from the parent study to this extension study, the duration between the last ATYR1940 dose in the parent study and first ATYR1940 dose in this extension study is 1 week; however, a maximum duration of 3 weeks is permissible. (A window >3 weeks may be permissible on a case-by-case basis, if required due to administrative reasons, after consultation with the Medical Monitor.) For the first 12 weeks in this extension study, patients will receive ATYR1940 at the highest tolerated dose received in the parent study; no dose adjustments are allowed during this 12-week period. After 12 weeks, if the patient is demonstrating good tolerability, the ATYR1940 dose may be increased on a patient-specific basis at the Investigator's discretion, in consultation with the Sponsor and Medical Monitor. ATYR1940 dose increases to >3.0 mg/kg are not permissible. All patients will receive ATYR1940 on a weekly basis in this study, regardless of the frequency of dosing in the parent study. ATYR1940 will be administered via IV infusion over 90 minutes. If medically indicated, the infusion duration and volume may be adjusted at the Investigator's discretion in consultation with the Medical Monitor and Sponsor.
Number of Patients Planned:	Based on the design of the parent studies, it is estimated that up to 24 patients will be enrolled in this study.
Diagnosis and Main Criteria for Inclusion:	Patients must meet all of the following criteria to be considered eligible for study entry: • Enrolled in and completed the treatment period in the parent study. • Demonstrated, in the Investigator's opinion, acceptable tolerability of ATYR1940. • In the Investigator's opinion, patient has shown acceptable compliance with ATYR1940 and the study procedures in the parent study and is willing and able to comply with all procedures in the current study. • Is, in the Investigator's and Sponsor's opinion, a suitable candidate for continued ATYR1940 treatment. • Provide written informed consent or assent (as appropriate, based on age of majority) after the nature of the study has been explained and prior to the performance of any research-related procedures.

Exclusion Criteria:

Patients meeting any of the following criteria are not eligible for study entry:

- At any time during participation in the parent study, met a ATYR1940 discontinuation criterion, including, but not limited to:
  - Jo-1 antibody (Ab) levels ≥1.5 U/mL.
  - Clinical evidence of a generalized infusion-related reaction (IRR) (see Section 7.5.5.1).
  - Clinical evidence of a National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) ≥Grade 2, study-drug-related serious adverse event (SAE).
  - Pregnancy.
  - Progression of disease that, in the opinion of the Investigator, precluded further participation in the study.
  - Withdrawal of consent or assent.
  - Other findings that, at the discretion of the Investigator and/or Sponsor, indicated that study drug administration should be discontinued.
- Is expected to require treatment with curcumin or systemic albuterol (intermittent inhaled albuterol is permissible) during study participation; or use of a product that putatively enhances muscle growth (e.g., insulin-like growth factor, growth hormone) or activity (e.g., Coenzyme Q, Coenzyme A, creatine, L-carnitine) on a chronic basis; or statin treatment initiation or significant adjustment to statin regimen (stable, chronic statin use is permissible).
- Planned to receive any vaccination during study participation.
- Abnormal baseline findings, medical condition(s), or laboratory findings that, in the Investigator's opinion, might jeopardize the patient's safety or decrease the chance of obtaining satisfactory data needed to achieve the objectives of the study.
- Evidence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematological, metabolic, dermatological, or gastrointestinal disease, or has a condition that requires immediate surgical intervention or other treatment or may not allow safe participation.
- If female and of childbearing potential (premenopausal and not surgically sterile), has a positive pregnancy test at entry or is unwilling to use contraception from the time of entry through the 3-month Follow-up visit. Acceptable methods of birth control include abstinence, barrier methods, hormones, or intra-

	uterine device. • If male, is unwilling to use a condom plus spermicide during sexual intercourse from the time of entry through the 1-month Follow-up visit.
Test Products, Doses, and Mode of Administration:	ATYR1940 is a 505 amino acid protein identical to the wild-type amino acids 2-506 of human histidyl tRNA synthetase (HARS). ATYR1940 is formulated at a target concentration of 25 mg/mL as a sterile, nonpyrogenic solution in a formulation buffer containing histidine, sodium chloride, and polysorbate 20 at pH 7.3 and filled into type 1 borosilicate glass vials (5 mL) with butyl rubber stoppers and aluminum seals. The fill volume of the clinical trial material is 4 mL. The product is non-preserved and is suitable for a single-dose use by IV administration. ATYR1940 will be administered via IV infusion. For the first 12 weeks in this extension study, patients will receive ATYR1940 at the highest tolerated dose received in the parent study; no dose adjustments are allowed during this 12-week period. After 12 weeks, if the patient is demonstrating good tolerability, the ATYR1940 dose may be increased on a patient-specific basis at the Investigator's discretion, in consultation with the Sponsor and Medical Monitor. ATYR1940 dose increases to >3.0 mg/kg are not permissible. The Sponsor has the discretion to delay dosing or decrease a patient's dose, based on relevant data reviewed concurrently in an individual patient (e.g., Jo-1 Ab levels) and/or additional clinical information provided by the Investigator. All patients will receive ATYR1940 on a weekly basis in this study, regardless of the frequency of dosing in the parent study. ATYR1940 will be administered IV as a 90-minute infusion. The ATYR1940 dose will be prepared for infusion in 100 mL (0.3 and 1.0 mg/kg) or 250 mL (3.0 mg/kg) saline as long as clinically indicated; refer to the Pharmacy Manual for details. During the course of the study, the Investigator may confer with the Medical Monitor and Sponsor if medically indicated or if there does not appear to be an increased risk to the patient, to decrease the study drug infusion time and/or volume of study drug administration on an individual patient basis.
Duration of Treatment:	Patients may be treated with ATYR1940 under this protocol until ATYR1940 is approved or its development is discontinued, the study is closed by the Sponsor, or a criterion for study drug discontinuation is met, as follows: • Jo-1 Ab levels ≥1.5 U/mL.

- Clinical evidence of a generalized IRR (see Section 7.5.5.1).
- Clinical evidence of an NCI CTCAE (version 4.03) ≥Grade 2, study-drug-related SAE.
- Pregnancy.
- Progression of disease that, in the opinion of the Investigator, precludes further participation in the study.
- Withdrawal of consent or assent.
- Other findings that, at the discretion of the Investigator and/or Sponsor, indicate that study drug administration should be discontinued.

Duration of Study: See above.

Study Endpoints:

Safety: Safety and tolerability will be evaluated by the following in all patients:

- Incidence of treatment-emergent adverse events (TEAEs) and SAEs overall and by intensity.
- Changes from baseline in:
  - Safety laboratory test results.
  - Electrocardiogram (ECG) findings.
  - Vital signs measurements.
  - Pulmonary evaluations (pulmonary function tests [PFTs] and pulse oximetry).
  - Incidence and level of anti-drug antibodies (ADA) titers and Jo-1 Ab levels.
- Exploratory characterization of immune response to ATYR1940.

Muscle Effects:

- Changes from baseline in the following clinical parameters:
  - Muscle disease burden on lower extremity skeletal muscle MRI.
  - Muscle strength, based on manual muscle testing (MMT).
  - Upper and lower extremity muscle function, based on the Brooke and Vignos scales, respectively.

Pharmacodynamics (Exploratory): The PD activity of ATYR1940 will be evaluated based on the following endpoints:

- Changes in muscular-dystrophy-related inflammatory immune state in peripheral blood, as assessed by:

	– Circulating immune proteins, such as cytokines. – *Ex vivo* inflammatory immune protein (including cytokines) release from peripheral blood mononuclear cells (PBMCs). – Immunophenotyping of circulating PBMCs. • Changes in serum- and/or plasma-based muscle biomarkers
Quality of Life (Exploratory):	Quality of life will be assessed, based on the Individualized Neuromuscular Quality of Life (INQoL) questionnaire and, for patients with FSHD, the FSHD-specific Health Inventory (FSHD-HI) questionnaire.
Systemic Exposure:	Systemic exposure will be determined through sparse pharmacokinetic (PK) sampling. As the data allow, PK parameters will be calculated from the drug concentration data using WinNonlin.
Sample Size Considerations:	No formal sample size calculation was performed for this extension study.
Statistical Methods:	Statistical analyses of safety, PK, and PD 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 Events:	The Schedule of Events is presented in Table 1.

Table 1: Schedule of Events

Assessment	Study Period / Frequency of Assessments								
	Treatment Period						Follow-up		
	Week 14 in Parent Study/ Week 1 in Current Study[1,2,3]	**Weekly (W2, W3, etc)**	**Monthly (Q4W) (Week 4, 8, etc)**	**Every 6 weeks (Q6W) (Week 6, 12, etc)**	**Every 3 Months (Q12W) (Week 12, 24, etc)**	**Every 6 Months (Q24W) Week 24, 48, etc.**	**1-week F/U**	**4-week F/U**	**12-week F/U**
Visit Window (days)	**-**	**±3D[4]**	**±3D[4]**	**±3D[4]**	**±5D[4]**	**±5D[4]**	**±3D**	**±3D**	**±5D**
Informed consent/assent	X[1]								
Confirm inclusion/exclusion criteria	X[1]								
Weight[5]	X				X		X	X	
Vital signs[6]	X[3]	X					X	X	X
Complete physical examination	X			X				X	
Surveillance skeletal muscle MRI	X				X[7]				X
ATYR1940 administration[8]	X[1]	X							
12-lead ECG[9]	X[3]		X				X	X	
Pulse oximetry[10]	X[1]	X					X	X	X
Pulmonary function tests[11]									
FEV_1, FVC, and FEV_1/FVC ratio	X[1]			X				X	
Total lung capacity and DLCO	X[1]				X			X	
Adverse events	X[3]	X					X	X	X
Prior/concomitant medications	X[3]	X					X	X	X
Manual muscle testing	X				X		X		

Assessment	Study Period / Frequency of Assessments								
	Treatment Period						Follow-up		
	Week 14 in Parent Study/ Week 1 in Current Study[1,2,3]	**Weekly (W2, W3, etc)**	**Monthly (Q4W) (Week 4, 8, etc)**	**Every 6 weeks (Q6W) (Week 6, 12, etc)**	**Every 3 Months (Q12W) (Week 12, 24, etc)**	**Every 6 Months (Q24W) Week 24, 48, etc.**	**1-week F/U**	**4-week F/U**	**12-week F/U**
Visit Window (days)	**-**	**±3D[4]**	**±3D[4]**	**±3D[4]**	**±5D[4]**	**±5D[4]**	**±3D**	**±3D**	**±5D**
Upper and lower extremity function[12]	X				X		X		
INQoL	X				X		X		X
FSHD-HI[13]	X[1]				X		X		X
Laboratory Assessments									
Pregnancy test[14]	X[3]		X					X	
Hematology, serum chemistries, and urine analysis with microscopy[15]	X		X				X	X	X
Plasma complement factors[16]	X[1]				X		X		
Serum complement and tryptase levels[17]	X[1]				X		X		
Jo-1 antibodies[18]	X	X					X	X	X
ADA[19]	X			X			X	X	X
HARS (human histidyl-tRNA synthetase; serum)	X							X	
Serum ATYR1940 concentrations[20]	X			X			X		
Muscle biomarkers	X[1]				X		X	X	
Biomarkers in blood	X				X		X	X	

Assessment	Study Period / Frequency of Assessments								
	Treatment Period						Follow-up		
	Week 14 in Parent Study/ Week 1 in Current Study[1,2,3]	**Weekly (W2, W3, etc)**	**Monthly (Q4W) (Week 4, 8, etc)**	**Every 6 weeks (Q6W) (Week 6, 12, etc)**	**Every 3 Months (Q12W) (Week 12, 24, etc)**	**Every 6 Months (Q24W) Week 24, 48, etc.**	**1-week F/U**	**4-week F/U**	**12-week F/U**
Visit Window (days)	**-**	**±3D[4]**	**±3D[4]**	**±3D[4]**	**±5D[4]**	**±5D[4]**	**±3D**	**±3D**	**±5D**
PBMCs for immunophenotyping (general and disease-related) and culture for immune protein release	X				X		X	X	
Assessments for Patients in Parent Study ATYR1940-C-003 Only									
Visual acuity	X[1]					X	X		X
Pure Tone Audiometry	X[1]					X	X		X

Note: On ATYR1940 administration days, laboratory samples are to be collected and assessments performed pre-infusion, unless otherwise specified.

1 Week 1 in the current study (ESW1) is equivalent to Week 14 in the parent study (PSW14). The Week 1 column in this table reflects assessments that are to be performed at ESW1 (cells with heavy weight borders) in addition to those performed at PSW14 (cells with regular weight borders), as indicated in the parent study protocol. All PSWeek 14/ESWeek 1 assessments are to be completed and eligibility is to be confirmed before the first ATYR1940 dose in the current study at ESW1.

2 A maximum duration of 3 weeks is permissible between the last ATYR1940 dose in the parent study (i.e., at Week 13) and the first ATYR1940 dose in the current study (at ESW1). A window >3 weeks may be permissible on a case-by-case basis, if required due to administrative reasons, after consultation with the Medical Monitor.

3 If there is >1 week (+3 days) between the last ATYR1940 dose in the parent study and the first ATYR1940 dose in the current study, the assessments indicated are to be repeated within 7 days before ESW1.

4 For scheduling purposes, a ±3-day window is permissible around ATYR1940 infusion; however, each ATYR1940 dose must be separated by at least 5 days and no more than 9 days and only 1 dose may be administered within a given study week; if a patient's scheduled visit day is changed in a given week (e.g., changed from Tuesday to Thursday), then subsequent weekly visits may be accordingly adjusted (e.g., Thursdays) or may revert back to the original schedule (e.g., Tuesdays), provided ATYR1940 is administered according to the timeframes specified. For the every 12-week and 6-month visits, a ±5-day window is permissible.

5 Weight is to be re-measured any time the Investigator suspects the patient has experienced a notable change in weight (±10%) and the ATYR1940 dose recalculated.

6 Vital signs are to be measured on weekly dosing days pre-infusion; every 30 minutes (±5 minutes) during the infusion; at the end of the infusion (±5 minutes); at 30 minutes (±5 minutes) after the end of infusion; and at additional time points as clinically indicated. Vital signs also must be measured within 7 days before ATYR1940 administration at ESW1. (On weekly dosing days, post-infusion vital sign measurements also will be collected before blood sample collection.) In addition, vital signs are to be measured in the event of a generalized IRR (see Section 8.5.9.4).

7 To be performed every 3 months (±1 week).

8 ATYR1940 will be administered via IV infusion over 90 minutes (-5 minutes, +15 minutes), unless it is determined by the Investigator in consultation with the Medical Monitor and Sponsor that a patient should receive a different dosing duration, as medically indicated.

9 A 12-lead ECG is to be performed on the designated dosing days prior to and 30 minutes (±15 minutes) following the end of infusion and once at the additional designated follow-up visits. A 12-lead ECG must be performed within 7 days before ATYR1940 administration at ESW1. In addition, ECGs are to be performed in the event of a generalized IRR (see Section 8.5.9.4).

10 Pulse oximetry is to be performed on weekly dosing days from 5 minutes prior to the start of infusion through 30 minutes (-5 minutes, +15 minutes) after the end of infusion; at the additional designated follow-up visits; and as clinically indicated if the patient experiences pulmonary signs or symptoms (e.g., chest tightness, increased respiratory rate). In addition, pulse oximetry is to be performed in the event of a generalized IRR (see Section 8.5.9.4)

11 Pulmonary function tests, including forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio are to be measured prior to infusion at Week 1; then on the designated dosing days (every 6 weeks) at 2.5 hours (±30 minutes) after the end of infusion; and at the designated follow-up visit. Total lung capacity and diffusion capacity of the lung for carbon monoxide (DLCO), are to be measured at Week 1; then on the designated dosing days (every 12 weeks); and at the designated follow-up visit. In addition, pulmonary function tests are to be conducted in the event of a generalized IRR (see Section 8.5.9.4).

12 Upper extremity function to be measured using the Brooke scale; lower extremity function to be measured using the Vignos scale.

13 The FSHD HI should be completed at the same time of day and before other assessments scheduled for that day, including the InQoL. The order of assessments should remain consistent throughout the study.

14 Urine pregnancy testing is required for females of childbearing potential (i.e., premenopausal and not surgically sterile) only. Pregnancy testing must be performed within 7 days before ATYR1940 administration at ESW1. Testing is to be performed using the local laboratory and before study drug infusion.

15 Clinical safety laboratory tests include clinical chemistry, hematology, and urine analysis with microscopy. On the designated dosing days, blood samples for safety laboratory tests are to be collected pre-infusion. Patients with evidence of a generalized IRR are to have additional safety laboratory tests performed, as described in Section 8.5.9.4.

16 Blood samples for complement factors in plasma (including C3a, C4a, C5a, Bb, and SC5b-9) will be collected on the designated dosing days prior to and 1.5 hours (±15 minutes) after the end of infusion and at the designated follow-up visit. In addition, samples for complement factors in plasma are to be collected in the event of a generalized IRR (see Section 8.5.9.4).

17 Blood samples for tryptase, C3, C4, and CH50 will be collected on the designated dosing days prior to and 1.5 hours (±15 minutes) after the end of infusion on the designated dosing days and at the designated follow-up visit. In addition, samples for assessment of tryptase, C3, C4, and CH50 are to be collected in the event of a generalized IRR (see Section 8.5.9.4).

18 Blood samples for assessment of Jo-1 Ab are to be collected on dosing days prior to initiation of infusion, and at the additional time points indicated. The Week 1 Jo-1 Ab sample must be obtained and result reviewed within 2 weeks prior to the first ATYR1940 dose. In addition, samples for assessment of Jo-1 Ab are to be collected in the event of a generalized IRR (see Section 8.5.9.4).

19 Blood samples for analysis of antidrug antibodies (ADA) are to be collected on the designated dosing days prior to initiation of infusion and at the additional time points indicated. Blood samples for assessment of ADA are to be collected in the event of a generalized IRR (see Section 8.5.9.4). For patients with elevated ADA at the 12-week F/U visit, additional ADA testing should be performed every 1 to 3 months until level returns to baseline.

20 Blood samples for assessment of ATYR1940 concentrations are to be collected on the designated dosing days at end of infusion and 4 hours after the start of infusion. ATYR1940 serum concentrations also are to be collected in the event of a generalized IRR (see Section 8.5.9.4).

LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	Antibody
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CA	Competent Authority
CK	Creatine kinase
C_{max}	Maximum serum concentration
CRA	Clinical Research Associate
CSS	Clinical Severity Score
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	Diffusion capacity of the lung for carbon monoxide
DMB	Data Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End-of-Study
ESW1	Week 1 in the extension study
EU	European Union

Abbreviation	Definition
FEV_1	Forced expiratory volume in 1 second
FSHD	Facioscapulohumeral muscular dystrophy
FSHD-HI	Facioscapulohumeral Muscular Dystrophy-Health Inventory
FVC	Forced vital capacity
GCP	Good Clinical Practice
HARS	Human histidyl tRNA synthetase
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational New Drug Application
INQoL	Individualized Neuromuscular Quality of Life
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	Intravenous
LGMD	Limb Girdle Muscular Dystrophy
LGMD2B	Limb Girdle Muscular Dystrophy 2B
MCP-1	Monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MMP-9	Matrix metallopeptidase 9

Abbreviation	Definition
MMT	Manual muscle testing
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
PBMCs	Peripheral blood mononuclear cells
PD	Pharmacodynamic(s)
PFT	Pulmonary function test
PK	Pharmacokinetic(s)
PSW14	Week 14 in the parent study
Q12W	Every 12 weeks
Q4W	Every 4 weeks
Q6W	Every 6 weeks
RBC	Red blood cell (count)
RMIC	Rare muscle diseases with an immune component
SAE	Serious adverse event
SAP	Statistical Analysis Plan
STIR	Short tau inversion recovery
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
t_{max}	Time to maximum serum concentration
TNF	Tumor necrosis factor
US	United States
WBC	White blood cell (count)

TABLE OF CONTENTS

LIST OF TABLES IN THE TEXT

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

Sponsor Signatory:

Sponsor Signatory
[redacted]
aTyr Pharma, Inc.
Mobile Telephone: [redacted]

Medical Monitor:

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

2. INTRODUCTION

The rare muscle diseases with an immune component (RMIC) represent a group of rare autoimmune and genetic muscle conditions characterized by inflammatory cell infiltration into muscle tissue. RMIC encompass the more severe and grave forms of diseases, such as polymyositis, dermatomyositis, sporadic inclusion body myositis, immune necrotizing myopathy, Duchenne's muscular dystrophy, limb girdle muscular dystrophy (LGMD), and facioscapulohumeral muscular dystrophy (FSHD). Many of the RMIC disorders are genetically-based and thus are defined and diagnosed by a combination of clinical signs and genetic analysis. Patients with RMIC suffer from debilitating muscle weakness and experience significant morbidity and, in some diseases, an increased mortality compared to the general population. As a group, RMIC are associated with tremendous patient suffering and constitute a high unmet medical need.[1,2]

2.1. Limb Girdle Muscular Dystrophy

Limb girdle muscular dystrophies are a group of uniformly progressive muscular dystrophies that share a common, but highly variable clinical presentation characterized predominantly by proximal weakness affecting the pelvic and shoulder girdles, and usually sparing the face. This group of disorders is currently being re-classified based on profound advances in the molecular genetics underlying these diseases. The various LGMD diseases are categorized by inheritance pattern, including those with dominantly inherited forms (i.e., LGMD1) and those with recessively-inherited forms (i.e., LGMD2). Within these categories, the diseases are further characterized by the causative genetic defect. Currently, LGMD is a collection of ~30 genetic muscle diseases caused by mutations at more than 50 genetic loci.[3] Because of the heterogeneity of LGMD and the lack of diagnostic specificity, there are few reports on the prevalence of LGMD; however, it is estimated to range from 1:14,500 to 1:123,000, depending on the genetically defined form (Genetics Home Reference 2015). The age of onset, severity, and features of LGMD vary among the subtypes. Overall, LGMD affects men and women equally.

LGMD2B is a recessively inherited dystrophy, often termed dysferlinopathy, since the causative mutations reside within the dysferlin gene (*DYSF*).[4] LGMD2B is characterized mainly by two distinct clinical phenotypes: LGMD syndrome, with early weakness and atrophy of the pelvic and shoulder girdle muscles in adolescence or young adulthood and with slow progression, and Miyoshi myopathy, with muscle weakness and atrophy in young adults, most marked in the distal parts of the legs, especially the gastrocnemius and soleus muscles. Over a period of years, the weakness and atrophy spread to the thighs and gluteal muscles. The forearms may become mildly atrophic, with decrease in grip strength, but the small muscles of the hands are spared. Two other phenotypes of LGMD2B that have been identified are less commonly seen, distal anterior compartment myopathy, a rapidly progressing form that presents in the third decade, with weakness of

the anterior tibialis muscles followed by severe weakness in the lower limbs followed by the upper limbs, and dysferlinopathy with rigid spine, which presents with lower limb weakness and atrophy in addition to contractures of the neck, chest, hip, and knee.[3] Although cardiomyopathy occurs in some forms of LGMD, this feature is not commonly seen in LGMD2B. LGMD2B, representing ~5% of patients with autosomal recessive LGMD, is one of the most common forms in the United States (US).[5,6]

There are multiple lines of evidence supporting a prominent role of inflammation in the pathophysiology of LGMD2B. The genetic mutations in dysferlin appear to create a defect in muscle membrane repair.[7] Alterations in this process likely create a pathophysiological environment in muscle that triggers an immune response. LGMD2B has been demonstrated to have a predominant immune cell-mediated pathology.[8,9] Patients with LGMD2B possess a dysregulated immune response, including cellular infiltration into affected muscle, increased expression of pro-inflammatory cytokines and altered cellular responses, including effects on myeloid cells.[10,11] Analysis of muscle biopsies from LGMD2B patients (including Myoshi myopathy, distal anterior compartment myopathy, and LGMD[12,13]), has revealed that the most prominent cellular immunophenotype in LGMD muscle is infiltration with CD4 > CD8 positive T-cells, and macrophages, cell types that are modulated by ATYR1940 (see Section 2.3). Cytokine patterns typically reflect Th1 and M1 differentiation processes, including interleukin (IL)-1β, interferon-γ, and tumor necrosis factor (TNF)-α. These characteristics are also reflected in mouse models of LGMD2B in which the dysferlin gene is mutated, including the requirement for T and B cells in disease[8], as well as the expression of pro-inflammatory cytokines.[14] Further, inhibition of inflammatory cytokines results in reduction in disease in dysferlin-deficient mice.[15,16] The muscle in patients with dysferlinopathy is characterized by massive immune cell infiltrates, and dysferlin-negative monocytes were shown to be aggressive and phagocytose more particles, suggesting that dysferlin deregulation in monocytes might contribute to disease progression.[10,13]

There currently is no pharmacologic treatment for the muscle disease in LGMD, including corticosteroids.[17] Thus, symptomatic patients are managed with palliative and supportive care, typically including physical, occupational, and exercise therapy and with physical support (e.g., canes, walkers) as needed. Investigation of gene therapies and cell transfer therapies for the treatment of this condition is ongoing; however, the efficacy and long-term safety of such therapies have not yet been established.[18] Furthermore, such therapies have immunologic complications as well as issues regarding mechanism of delivery to muscles throughout the body.[19]

The predominant role of the immune system in LGMD2B suggests that focusing on the inflammatory status of muscles in patients *a priori* in a clinical study could increase the likelihood of seeing an impact of non-corticosteroid immunomodulator.

2.2. Facioscapulohumeral Muscular Dystrophy

FSHD is a rare, debilitating genetic myopathy. The primary clinical phenotype of FSHD patients is progressive skeletal muscle weakness that develops in a descending, asynchronous pattern.[20,21] Weakness usually starts with muscles in the face and neck, and moves to the shoulder girdle, upper arms, trunk, and legs. As weakness progresses, musculoskeletal deformities (e.g., scapular winging, hyperlordosis, and kyphoscoliosis) develop, and mobility becomes severely compromised.

Inflammation as an early event and single muscle involvement has been proposed to play a role in FSHD pathophysiology.[22] The infiltrative inflammatory process includes invasion of CD4 and CD8 T cells, B lymphocytes and monocytes, particularly into skeletal muscles that are in the early stages of disease.[22] Once disease progresses in a particular muscle, weakness ensues and dystrophic changes, including necrosis, phagocytosis, regeneration, variation in fiber size, and proliferation of connective tissues with fatty infiltration/replacement, can eventually be seen.[23]

There are currently no pharmacological interventions for this disease worldwide.

Although it is the most common genetic muscular dystrophy, FSHD is a rare disease, with an estimated prevalence of 1 in 15,000 to 20,000.[21,24] FSHD typically presents in adolescence to early adulthood, and up to 20% of patients become wheelchair dependent after age 50.[21] Less frequently, clinical signs and symptoms of FSHD are evident earlier in childhood, including during the first decade of life. Classification of FSHD by age of onset into early and late presentation is noted in the literature, although the nomenclature is variable. Infantile onset FSHD, which comprises less than 5% of all cases of FSHD, has been classified as early onset FSHD, and a commonly cited definition for it – facial weakness prior to 5 years of age and shoulder girdle weakness prior to 10 years of age – was applied in a study by Brouwer and colleagues[25] and has been adopted by others. This early onset FSHD phenotype is characterized by more severe, rapidly progressive muscle involvement, often resulting in wheelchair dependence by the end of the first decade.[26] Although subclinical extramuscular manifestations of FSHD involving the eye (retinal vasculopathy, characterized by telangiectatic blood vessels and microaneurysms on fluorescein angiography, but without loss of vision) and ear (high frequency hearing loss) occur relatively frequently in patients with FSHD,[27] patients with infantile onset FSHD appear to be more commonly susceptible to severe extramuscular involvement at a young age.[25,26] For example, sensorineural hearing loss in infantile onset FSHD is progressive and may affect language and social development in these patients. In some patients, an exudative retinopathy, described as Coats syndrome,[28] presents the potential for retinal detachment and vision loss, if uncorrected. Therefore, auditory and ophthalmic screening and/or monitoring, and intervention, where feasible, are recommended in pediatric patients with infantile onset FSHD.

There is limited published literature describing other early onset patients with FSHD who do not meet criteria for the phenotype described by Brouwer et al.[25], but who have symptom onset within approximately the first decade of life. This group of patients may also be considered to have early onset FSHD, distinguished by age at presentation; however, it is unclear if this group of early onset FSHD patients follows a clinical course similar to that classically reported in adults, or if there may be distinct phenotypes within this population.

FSHD became a genetically defined muscular dystrophy with the discovery of the molecular genetics of FSHD1[29] and FSHD2.[30] Over 90% of FSHD patients are considered to have FSHD1, a dominantly inherited disease that maps to variable sized deletions of a repeated microsatellite array (*D4Z4*) in the sub-telomeric region of chromosome 4q35. Normal, unaffected individuals have from 11 to 100 of these array repeats, while those with FSHD1 have only 1 to 10 repeats.[29] Individuals with the fewest array repeats within this range (1-3) tend to have earlier-onset disease and more rapid disease progression.[31,32]

FSHD2, a second form that affects approximately 5% of patients, results from a mutation in the chromatin modulator gene, *SMCHD1* on chromosome 18. The inheritance pattern of FHSD2 can be considered "di-genic", because as in FSHD1, a permissive 4q35 haplotype that generates a novel polyadenylation signal distal to the *D4Z4* repeat array is required for disease penetrance.[30]

There is considerable variability in onset and disease progression in individuals with FSHD1 and 2. An epigenetic basis (interindividual differences in CpG methylation at D4Z4) for this basis has been recently uncovered.[33]

Since the identification of these genetic etiologies of FSHD, a primary focus on the pathogenesis of FSHD has been on the *D4Z4* repeat. This deoxyribonucleic acid sequence contains a copy of *DUX4*, a transcription factor gene normally expressed in germ line development, but repressed in somatic tissue such as skeletal muscle.[34] It has been hypothesized that contracted *D4Z4* repeat arrays in FSHD1, or specific *SMCHD1* mutations in FSHD2 set the stage for the FSHD phenotype by establishing a "relaxed chromatin state" that results in somatic cell de-repression of *DUX4* expression, particularly in skeletal muscle.[21,29,35] Mis-regulated, ectopic expression of numerous *DUX4* regulated genes then occurs, leading to transcriptional profiles associated with abnormal muscle regenerative, vascular and immune responses. Aspects of these profiles have been linked to the immunopathology observed in patients with FSHD.[36]

Although the genetic basis for the disease has been defined, and the pattern of muscle involvement in FSHD generally is predictable, the particular muscles involved are not. For example, a single muscle in a limb or the trunk may be severely affected while for reasons that are unclear, an adjacent muscle will be either affected later in the disease course or spared completely.

Inflammatory and dystrophic disease processes can be followed in individual muscles using magnetic resonance imaging (MRI), a methodology of increasing utility for monitoring the progression of muscular dystrophies.[22,37,38,39] The T1-weighted signal intensity by MRI is believed to represent fatty infiltration, while the short tau inversion recovery (STIR) signal intensity suggests the presence of inflammation. This increase in signal intensity is due to an increase in the T2 relaxation time, which can be measured using quantitative MRI.[38,40] A recent study with FSHD patients and controls found inflammation (CD8+ and CD4+ T cells), specifically in muscle biopsies taken from STIR hyperintense muscles.[22] Longitudinal MRI studies have recently shown that inflammatory changes in FSHD skeletal muscle directly precede fatty infiltration.[41] In addition, the degree of fatty infiltration as determined by the number of T1-positive muscles has been correlated with a commonly used measure of functional status, the FSHD clinical severity score (CSS).[22] These data suggest that MRI findings could be highly informative in clinical studies in FSHD patients.[21,22]

The inflammatory immune response in FSHD is also reflected in the peripheral circulation of individuals with FSHD through several lines of evidence. First, in FSHD patients with muscle inflammation detected by STIR positive MRI, activated immune cells (CD8+ T cells [pSTAT1+, T-bet+] and CD14+pSTAT1+ cells) are present in the circulation. Peripheral blood mononuclear cells (PBMCs) from individuals with STIR positive muscle also show evidence of activation in cell culture by spontaneously releasing high amounts of immune proteins such as IL-10, IL-6, TNF-α and IL-12p40 into the culture medium compared to controls.[22]

In other studies of the inflammatory immune state of FSHD patients, elevated levels of circulating immune proteins, including monocyte chemoattractant protein-1 (MCP-1), epidermal growth factor, matrix metallopeptidase 9 (MMP-9), creatine kinase-myocardial band, and tissue plasminogen activator, are seen in FSHD patients compared to control, unaffected individuals.[42]

There currently are no pharmacologic treatments for the muscle disease in FSHD. Furthermore, there are no validated animal models in this disease for use in drug development.[43] However, both the dystrophic changes and the inflammatory process have been considered rational disease targets.[22] To date, a small number of drugs with potential impact either on the inflammatory response or the muscle itself have been evaluated in FSHD in clinical studies, albeit without positive results. These included the non-specific immunosuppressant, prednisone,[44] and molecules that are thought to enhance muscle mass: beta adrenergic agonists,[45] creatine monohydrate supplementation, and myostatin inhibitors.[46] In these clinical studies, no clinically meaningful benefit was observed. However, no effort was made to stratify the patients based on the degree of inflammation or specific muscle involvement.

Recent data in FSHD suggest that focusing on the inflammatory status of muscles in patients *a priori* in a clinical study could increase the likelihood of seeing an impact of an immune modulator.[22]

2.3. ATYR1940

ATYR1940 is a protein therapeutic candidate identical to amino acids 2-506 of wild-type human histidyl tRNA synthetase (HARS). ATYR1940 does not belong to any established therapeutic class. ATYR1940 is a preservative-free liquid concentrate (4.0 mL) supplied at a concentration of approximately 25 mg/mL in a 5 mL single-use type 1 glass vial that is further diluted with 0.9% normal saline for intravenous (IV) administration.

Non-clinical studies in animals have shown that IV administered ATYR1940 is efficacious in various immune driven disease models in an active dose range of 1.0 to 3.0 mg/kg, including normalization or reduction of severe statin-induced skeletal myopathy, as indicated by improved muscle histology (decreased inflammatory cell infiltration, necrotic fibers and fibrotic changes compared to control); decreased muscle protein levels in serum (e.g., decreased skeletal troponin I); decreased cellular infiltration (decreased $CD68^{+}$ cells by immunohistochemistry [IHC], decreased CD11b and CD14 messenger ribonucleic acid [mRNA; macrophage lineage]; decreased $CD3^{+}$ cells by IHC, CD8a and CD8b mRNAs [T cells] and increased $myeloperoxidase^{high}$ by IHC [neutrophil marker]); and decreased inflammatory marker levels in skeletal muscle tissues (e.g., decreased IL-6, MCP-1, and MMP-9). These data support the role of HARS in modulating immune responses in skeletal muscle, and the potential of ATYR1940 to therapeutically suppress inflammatory cell infiltration (such as CD8+ cells) into skeletal muscles, thereby attenuating skeletal muscle fiber atrophy and circulating evidence of muscle disease, including pathologic serum levels of creatine kinase (CK) and other muscle proteins in patients with FSHD and other RMIC disorders.

Nonclinical studies in immune cells isolated from the blood of healthy subjects have shown direct immune modulatory effects of ATYR1940, including attenuation of cytokines released from stimulated T cells and decreased spontaneous release of cytokines from M1 macrophages differentiated in the presence of ATYR1940.

Clinical data with ATYR1940 are available from one completed study in healthy volunteers; limited clinical data are available from ongoing studies in patients with muscular dystrophies.

The completed healthy volunteer study included 24 healthy subjects who tested negative for antibodies against HARS (i.e., Jo-1 antibody [Ab]) exposed to a single IV dose of ATYR1940 in a Phase 1, first-in-human, randomized, double blind, placebo-controlled, single ascending dose study (ATYR1940-C-001). In this study, ATYR1940 was investigated at doses of 0.1, 0.3, 1.0, and 3.0 mg/kg. Within each dose cohort, 6 subjects received ATYR1940 and 2 subjects received placebo. A single, 30-minute IV infusion of

ATYR1940 0.1 to 3.0 mg/kg was safe and well tolerated by healthy subjects. All adverse events (AEs) were mild in severity, non-serious, and transient. Overall, treatment-emergent AEs (TEAEs) reported for more than 1 ATYR1940-treated subject included dizziness, headache, abdominal distension, fatigue, nasopharyngitis, nausea, and oropharyngeal pain. No dose relationship was apparent with regard to the occurrence of these AEs. Furthermore, no clinically relevant changes from baseline in safety laboratory tests, vital signs, electrocardiograms (ECGs), pulmonary function tests (PFTs), or arterial oxygen saturation (based on pulse oximetry) were observed. Six ATYR1940-treated subjects were determined to be anti-drug-antibody (ADA) positive at at least one post-dose time point; one of these subjects also was ADA positive at baseline. ADA positivity was not associated with any temporal adverse systemic symptoms, safety laboratory abnormalities, or abnormal spirometry or pulse oximetry findings in any of these subjects. Furthermore, the pharmacokinetics (PK) of ATYR1940 was not altered in these subjects.

Results of PK analyses from Study ATYR1940-C-001 revealed evidence of systemic exposure to ATYR1940 in all treated subjects at all dose levels. Following an approximate 30-minute IV infusion of ATYR1940, peak serum concentrations generally occurred at or shortly after the end of infusion, with a mean time to attain maximum serum concentration (t_{max}) of approximately 0.5 hours, followed by a mono-phasic decline. Mean ATYR1940 exposure increased with increasing dose in a dose proportional manner. Mean maximum serum concentration (C_{max}) values increased approximately 24-fold over a 30-fold dose range, with mean C_{max} values of 603, 1470, 5480, and 14,700 ng/mL at doses of 0.1, 0.3, 1.0, and 3.0 mg/kg, respectively. Mean $AUC_{0\text{-}inf}$ was 3050, 7090, 28,800, and 77,500 ng*h/mL at doses of 0.1, 0.3, 1.0, and 3.0 mg/kg, respectively. Mean total systemic clearance was low (ranging from approximately 0.6-0.8 mL/min/kg) and the volume of distribution was small (approximately 0.2 L/kg), resulting in a terminal half-life ($t_{1/2}$) of approximately 3-6 hours across all dose levels. No pharmacodynamic (PD) effects of ATYR1940 were observed in this single-dose healthy subject study.

Limited data are available from the first clinical investigation of ATYR1940 in patients with FSHD, Study ATYR1940-C-002, "A Placebo-Controlled, Randomized, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Biological Activity of ATYR1940 in Adult Patients with Molecularly Defined Genetic Muscular Dystrophies". This study is being conducted in adult patients with FSHD at multiple sites in Europe (EU) and the US. In this study, patients are randomized (3:1) to receive ATYR1940 or placebo at doses of 0.3 or 1.0 for 4 weeks or 3.0 mg/kg for 12 weeks in sequential dose cohorts; qualified patients have the option to continue or initiate (i.e., in the case of patients randomized to the placebo group) ATYR1940 treatment in an ongoing extension study (ATYR1940-C-005).

Generalized infusion-related reactions (IRRs) have been reported for 3 patients treated in studies of ATYR1940, including one event that was considered serious. These events were observed following more than 4 weeks of dosing with 3.0 mg/kg ATYR1940 as a 30-minute, 50-mL IV infusion once weekly, and resolved after stopping the infusion and, in some instances, administering medications and IV fluids. Patients who experienced generalized IRRs were permanently discontinued from dosing.

The Sponsor has initiated the "parent" studies (Study ATYR1940-C-003 and ATYR-C-004) to this extension study. Study ATYR1940-C-003 is entitled "An Open-Label, Intrapatient Dose-Escalation Study to Evaluate the Safety, Tolerability, Immunogenicity, and Biological Activity of ATYR1940 in Patients With Early Onset and Other Pediatric Onset Facioscapulohumeral Muscular Dystrophy" and is being conducted in the US and EU. Study ATYR1940-C-004 is entitled "An Open-Label, Intrapatient Dose Escalation Study to Evaluate the Safety, Tolerability, Immunogenicity, and Biological Activity of ATYR1940 in Patients with Limb Girdle and Facioscapulohumeral Muscular Dystrophies". In both studies, which are being conducted in the US and EU, patients receive ATYR1940 for 12 weeks. Patients who were enrolled in Study ATYR1940-C-004 or in Stage 1 of Study ATYR1940-C-003 and meet the entry criteria may participate in this extension study and continue treatment with weekly ATYR1940. Patients may be treated with ATYR1940 under this protocol until ATYR1940 is approved or its development is discontinued, the study is closed by the Sponsor, or a criterion for study drug discontinuation is met (see Section 6.4.1).

2.4. Rationale for Current Study

aTyr has shown that: 1) HARS is detected in blood samples from healthy individuals and patients (preclinical work) and in the ATYR1940-C-001 study in blood samples from healthy subjects participating in the study and 2) human skeletal muscle cells release HARS during differentiation, a process that can be regulated by molecules already known to modulate muscle mass and blocked by antibodies to HARS. Furthermore, pharmacological application of ATYR1940 1) alters cytokine and other immune protein release from human primary immune cells, and 2) has immune modulatory activity in rodent models, including a rat model of myopathy. Taken together, HARS is a physiologically relevant modifier of muscle cell biology, and the ATYR1940 nonclinical data suggest that it may have therapeutic effect in patients with inflammatory muscle diseases, including FSHD, by modulating both immune and muscle cell responses.

LGMD2B and FSHD are chronic diseases that will likely require lifelong therapy. In the parent studies, ATYR1940 is administered over a relatively short period of up to 12 weeks (including weekly dosing in the ATYR1940-C-003 study and weekly and twice weekly dosing in the ATYR1940-C004 study). No maximum duration of therapy has been set in the current study, and patients will be allowed to receive treatment with ATYR1940 until ATYR1940 is approved or its development is discontinued, the study is

closed by the Sponsor, or a criterion for study drug discontinuation is met (see Section 6.4.1). The safety and efficacy of longer term exposure to ATYR1940 will be continuously assessed over the course of this extension study.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Objectives

The objectives of the study are to:

- Evaluate the safety, tolerability, and immunogenicity of long-term treatment with IV ATYR1940 in patients with LGMD2B or FSHD previously enrolled in clinical study ATYR1940-C-003 (Stage 1 only) or ATYR-1940-C-004.
- Explore the biological and PD activity of ATYR1940 in patients with LGMD2B and FSHD, based on changes in:
  - Serum-based muscle biomarkers.
  - Inflammatory immune state in peripheral blood.
  - Muscle disease and muscle disease burden, based on skeletal muscle MRI.
  - Skeletal muscle strength.
  - Upper and lower extremity muscle function.
  - Quality of life measures.

3.2. Study Endpoints

3.2.1. Safety and Tolerability Endpoints

The safety and tolerability endpoints of this study are:

- Incidence of TEAEs and serious adverse events (SAEs) overall and by intensity.
- Changes from baseline in:
  - Safety laboratory test results.
  - ECG findings.
  - Vital signs measurements.
  - Pulmonary evaluations (PFTs and pulse oximetry).
- Incidence and level of ADA titers and Jo-1 Ab levels.
- Exploratory characterization of immune response to ATYR1940.

3.2.2. Muscle Effects

Muscle strength and function will be evaluated by the following:

- Muscle disease burden on lower extremity skeletal muscle MRI.
- Muscle strength, based on manual muscle testing (MMT).
- Upper and lower extremity muscle function, based on the Brooke and Vignos scales, respectively.

3.2.3. Pharmacodynamics (Exploratory)

The PD effects of ATYR1940 will be evaluated by the following:

- Changes in muscular-dystrophy-related inflammatory immune state in peripheral blood, as assessed by:
  - Circulating immune proteins, such as cytokines.
  - *Ex vivo* inflammatory immune protein (including cytokines) release from PBMCs.
  - Immunophenotyping of circulating PBMCs.
- Changes in serum- and/or plasma-based muscle biomarkers.

3.2.4. Quality of Life (Exploratory)

Quality of life will be assessed based on the following:

- Individualized Neuromuscular Quality of Life (INQoL) questionnaire.
- For patients with FSHD, the FSHD-specific Health Inventory (FSHD-HI) questionnaire.

Specific endpoints based on quality of life data have not been defined.

3.2.5. Systemic Exposure

Systemic exposure will be determined through sparse PK sampling. As the data allow, PK parameters will be calculated from the drug concentration data using WinNonlin.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

Study ATYR1940-C-006 is a multi-national, multi-center, open-label extension study designed to evaluate the long-term safety, effects on muscle, and PD of ATYR1940 in patients with LGMD2B and FSHD previously treated in the parent studies. This study will be conducted at the same study centers at which patients were enrolled in the parent studies.

Patients who participated in and completed the treatment period in the parent study; in the Investigator's opinion, demonstrated acceptable tolerability of ATYR1940, are considered by the Investigator to be compliant with ATYR1940 and the study procedures, and do not meet any criterion for ATYR1940 discontinuation are eligible for participation in the current study, contingent upon Investigator and patient agreement to continue ATYR1940 treatment.

Ideally, when a patient transfers from the parent study to this extension study, the duration between the last ATYR1940 dose in the parent study and first ATYR1940 dose in this extension study is 1 week; however, a maximum duration of 3 weeks is permissible. (A window >3 weeks may be permissible on a case-by-case basis, if required due to administrative reasons, after consultation with the Medical Monitor.)

For the first 12 weeks in this extension study, patients will receive ATYR1940 at the highest tolerated dose received in the parent study; no dose adjustments are allowed during this 12-week period. After 12 weeks, if the patient is demonstrating good tolerability, the ATYR1940 dose may be increased on a patient-specific basis at the Investigator's discretion, in consultation with the Sponsor and Medical Monitor. ATYR1940 dose increases to >3.0 mg/kg are not permissible.

All patients will receive ATYR1940 on a weekly basis in this study, regardless of the frequency of dosing in the parent study.

ATYR1940 will be administered via IV infusion over 90 minutes. If medically indicated, the infusion duration and volume may be adjusted at the Investigator's discretion in consultation with the Medical Monitor and Sponsor.

4.2. Justification for the Study Design

ATYR1940 is being developed for rare, severe, muscle diseases with an immune component (i.e., RMIC), for which few, if any, efficacious treatment options exist, and no efficacious pharmacological therapies are approved. Given the significant unmet medical need in these disorders, and in LGMD2B and FSHD, in particular, advancing safe and efficacious therapies into patients as rapidly as possible is warranted.

The current study allows for patients who have demonstrated acceptable tolerability of ATYR1940 and who are candidates for continued treatment, in the Investigator's

opinion, to start or continue ATYR1940 until ATYR1940 is approved or its development is discontinued, the study is closed by the Sponsor, or a criterion for study drug discontinuation is met. As all patients will receive ATYR1940, it will be given in an open-label fashion.

The study includes ADA and Jo-1 Ab testing, detailed clinical monitoring for potential generalized IRRs, extended safety follow-up, and a specific plan to assist investigators in the clinical management of patients in whom clinical signs of generalized IRRs occur (see Section 7.5.5).

5. STUDY POPULATION

Based on the design of the parent studies, it is estimated that up to 24 patients will be enrolled in this study.

5.1. Inclusion Criteria

Patients must meet all of the following criteria to be considered eligible for study entry:

1. Enrolled in and completed the treatment period in the parent study.
2. Demonstrated, in the Investigator's opinion, acceptable tolerability of ATYR1940.
3. In the Investigator's opinion, patient has shown acceptable compliance with ATYR1940 and the study procedures in the parent study and is willing and able to comply with all procedures in the current study.
4. Is, in the Investigator's and Sponsor's opinion, a suitable candidate for continued ATYR1940 treatment.
5. Provide written informed consent or assent (as appropriate, based on age of majority) after the nature of the study has been explained and prior to the performance of any research-related procedures.

5.2. Exclusion Criteria

Patients meeting any of the following criteria are not eligible for study entry:

1. At any time during participation in the parent study, met a ATYR1940 discontinuation criterion, including, but not limited to:
    a. Jo-1 Ab levels ≥1.5 U/mL.
    b. Clinical evidence of a generalized IRR (see Section 7.5.5.1).
    c. Clinical evidence of a National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) ≥Grade 2, study-drug-related SAE.
    d. Pregnancy.
    e. Progression of disease that, in the opinion of the Investigator, precluded further participation in the study.
    f. Withdrawal of consent or assent.
    g. Other findings that, at the discretion of the Investigator and/or Sponsor, indicated that study drug administration should be discontinued.
2. Is expected to require treatment with curcumin or systemic albuterol (intermittent inhaled albuterol is permissible) during study participation; or use of a product

that putatively enhances muscle growth (e.g., insulin-like growth factor, growth hormone) or activity (e.g., Coenzyme Q, Coenzyme A, creatine, L-carnitine) on a chronic basis; or statin treatment initiation or significant adjustment to statin regimen (stable, chronic statin use is permissible).

3. Planned to receive any vaccination during study participation.
4. Abnormal baseline findings, medical condition(s), or laboratory findings that, in the Investigator's opinion, might jeopardize the patient's safety or decrease the chance of obtaining satisfactory data needed to achieve the objectives of the study.
5. Evidence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematological, metabolic, dermatological, or gastrointestinal disease, or has a condition that requires immediate surgical intervention or other treatment or may not allow safe participation.
6. If female and of childbearing potential (premenopausal and not surgically sterile), has a positive pregnancy test at entry or is unwilling to use contraception from the time of entry through the 3-month Follow-up visit. Acceptable methods of birth control include abstinence, barrier methods, hormones, or intra-uterine device.
7. If male, is unwilling to use a condom plus spermicide during sexual intercourse from the time of entry through the 1-month Follow-up visit.

5.3. Source of Patients

This will be a multinational, multi-center study. Each study center is required to obtain local Institutional Review Board (IRB)/Ethics Committee (EC) and national regulatory approval to conduct the study before enrollment of patients may commence. Patients who previously participated in Study ATYR1940-C-003 (Stage 1 only) or ATYR1940-C-004 and who meet the entry criteria of the current study will be eligible for enrollment.

6. STUDY CONDUCT

6.1. Patient Identification, Enrollment, and Randomization

Patients will be identified by a unique, 5-digit identification (ID) number consisting of the parent study number (i.e., "3" or "4"), a 1-digit site number, and the 3-digit patient numbers assigned in the parent study. For example, Patient [redacted] in parent study ATYR1940-C-003 would be renumbered as Patient [redacted] in this extension study.

Consented patients who satisfy all entry criteria will be enrolled into the study.

Randomization is not applicable to this study. Patients who qualify for the study will be enrolled in the study at Week 1 and study drug will be dispensed to the patient.

6.2. Patient Management

All patients must provide written informed consent or assent, as appropriate, based on local age of majority, before the performance of any study-related procedures. Patients who are determined to be eligible for the study will be enrolled into the study at the baseline visit (Week 1) and will receive IV infusions of ATYR1940 weekly. Patients will attend posttreatment follow-up visits 1, 4, and 12 weeks following completion of dosing. The 12-week follow-up visit is the End-of-Study (EOS) visit.

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.

6.4. Withdrawal and Replacement of Patients

6.4.1. Study Drug Discontinuation Criteria

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

- Jo-1 Ab levels ≥1.5 U/mL. Refer to Section 7.5.5 for complete details regarding the management of potential immunogenicity.
- Clinical evidence of a generalized IRR (see Section 7.5.5.1). Refer to Section 7.5.5 for complete details regarding the management of potential immunogenicity.

- Clinical evidence of an NCI CTCAE (version 4.03) ≥ Grade 2, study-drug-related SAE.
- Pregnancy.
- Progression of disease that, in the opinion of the Investigator, precludes further participation in the study.
- Withdrawal of consent or assent.
- Other findings that, at the discretion of the Investigator and/or Sponsor, indicate that study drug administration should be discontinued.

All patients who have been dosed with any amount of ATYR1940 will continue to be followed for safety. Patients who discontinue ATYR1940 dosing at any time during the treatment period should return to the study center for the 1-, 4-, and 12-week posttreatment follow-up visits and as clinically indicated.

Patients who discontinue ATYR1940 due to a generalized IRR or Jo-1 Ab levels ≥1.5 U/mL are to return to the study center for weekly visits as clinically indicated for safety follow up. At a minimum, such patients must attend the 1-, 4-, and 12-week posttreatment follow-up visits (see Section 7.5.5).

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

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 withdraw from the study 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 ATYR1940 or protocol requirements.
- Patient unwillingness to continue in the study.
- Any other reason, based upon the medical judgment of the Investigator.

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

At the time of discontinuation from the study, patients are to have all the assessments planned for the 1- and 4-week posttreatment follow-up visits performed within 7-days after the last study drug dose, if feasible. (Note that some assessments are listed in both the 1- and 4-week follow-up visit; such assessments need only to be performed once at the time of discontinuation.)

Patients who are withdrawn from the study for any reason will not be replaced.

6.5. Study Completion

A patient is considered to have completed the study if they complete the EOS visit.

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 suspend or discontinue development of ATYR1940.

6.7. Investigator Compliance

Study centers that deviate significantly from the protocol without prior approval from the Sponsor and regulatory authorities may be discontinued from the study. The Investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of ATYR1940, 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 Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidance documents.

7. STUDY DRUG

aTyr or designee will supply ATYR1940 to the pharmacies at all participating study centers.

7.1. Study Drug Supply

ATYR1940 is a 505 amino acid protein identical to the wild-type amino acids 2-506 of human HARS. ATYR1940 is formulated at a target concentration of 25 mg/mL as a sterile, non-pyrogenic solution in a formulation buffer containing histidine, sodium chloride, and polysorbate 20 at pH 7.3 and filled into type 1 borosilicate glass vials (5 mL) with butyl rubber stoppers and aluminum seals. The fill volume of the clinical trial material is 4 mL. The product is non-preserved and is suitable for a single-dose use by IV administration.

7.2. Study Drug Packaging and Labeling

ATYR1940 will be packaged in boxes containing vials of ATYR1940. The pharmacist will dilute ATYR1940 in saline, based on each patient's body weight, and transfer the dose to be administered to an infusion set.

Study drug labels will not bear any statement that is false or misleading in any manner or represents that the ATYR1940 is safe or effective for the purposes for which it is being investigated. The content of the labeling will be in accordance with local regulatory specifications and requirements.

7.2.1. Procedures for Breaking the Blind

This is an open-label study.

7.3. Study Drug Storage

ATYR1940 is to be stored in a locked area, accessible only to appropriate study personnel.

ATYR1940 is to be stored in a freezer at -20°C ± 5°C. Prior to preparation for administration, ATYR1940 is to be thawed in the refrigerator for 3 to 72 hours. The infusion set containing ATYR1940 is to be prepared just before use and should not be placed at room temperature for more than 6 hours.

ATYR1940 is for single-use administration and does not contain any preservatives or anti-microbial or bacteriostatic agents.

7.4. Study Drug Accountability

The Investigator or delegate will maintain accurate records of receipt and condition of ATYR1940, including dates of receipt. In addition, accurate records will be kept of the date administered, quantity administered, and the patient to whom ATYR1940 was

administered. Any reasons for departure from the protocol-specified dispensing regimen must also be recorded.

The Investigator is responsible for the accountability of all used and unused ATYR1940 vials. The site ID number and patient initials are to be recorded on each ATYR1940 accountability log. Each time study personnel dispense ATYR1940 for a patient, they are to record the date dispensed, amount dispensed, and their initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused supplies.

A Clinical Research Associate (CRA) will review ATYR1940 accountability records during routine monitoring visits. At the completion of the study, there will be a final reconciliation of all ATYR1940 vials.

7.5. Study Drug Dose and Administration

7.5.1. Dose and Route of Administration

ATYR1940 will be administered via IV infusion.

For the first 12 weeks in this extension study, patients will receive ATYR1940 at the highest tolerated dose received in the parent study; no dose adjustments are allowed during this 12-week period. After 12 weeks, if the patient is demonstrating good tolerability, the ATYR1940 dose may be increased on a patient-specific basis at the Investigator's discretion, in consultation with the Sponsor and Medical Monitor. ATYR1940 dose increases to >3.0 mg/kg are not permissible.

All patients will receive ATYR1940 on a weekly basis in this study, regardless of the frequency of dosing in the parent study.

7.5.2. Infusion Rate and Volume

ATYR1940 will be administered IV as a 90-minute infusion.

The ATYR1940 dose will be prepared for infusion in 100 mL (0.3 and 1.0 mg/kg) or 250 mL (3.0 mg/kg) saline, as long as clinically indicated; refer to the Pharmacy Manual for details.

During the course of the study, the Investigator may confer with the Medical Monitor and Sponsor if medically indicated or if there does not appear to be an increased risk to the patient, to decrease the study drug infusion time and/or volume of study drug administration on an individual patient basis. In such cases, the change(s) should be clearly documented in drug accountability records.

Body weight obtained at Week 1 will be used for preparation of each patient's mg/kg ATYR1940 dose. If the patient has a notable change in body weight (±10%) during the study, the Medical Monitor is to be notified regarding recalculation of ATYR1940 dose.

7.5.3. Dosing Frequency and Treatment Intervals

All patients will receive ATYR1940 weekly.

Samples for determination of Jo-1 Ab levels will be collected before each ATYR1940 dose; the Jo-1 Ab level from the previous dose will be used for the acceptability of dosing on each dosing day. ATYR1940 is to be permanently discontinued for any patient with a Jo-1 Ab level ≥1.5 U/mL.

7.5.4. Dose Reduction

If, in the Investigator's judgment, the patient is not tolerating a dose level, the Medical Monitor is to be contacted regarding the potential for dose reduction to a lower ATYR1940 dose level, or discontinuation of treatment (e.g., as would be the case for a generalized IRR), as appropriate.

The Sponsor has the discretion to delay dosing, change infusion duration, or decrease a patient's dose, based on relevant data reviewed concurrently in an individual patient (e.g., Jo-1 Ab levels) and/or additional clinical information provided by the Investigator.

7.5.5. Clinical Management Plan for Potential Immunogenicity

7.5.5.1. Infusion-Related Reactions

Generalized IRRs have been reported for 3 patients treated in studies of ATYR1940, including one event that was considered serious. The constellation of symptoms in these patients has varied, but the overarching diagnosis is IRR of a generalized nature (i.e., not at the site of injection), which occurred during the infusion of ATYR1940, but only after the patient had received multiple doses of ATYR1940. The IRRs occurred in the setting of infusing ATYR1940 over 30-minutes in 50 mL of normal saline. These reactions resolved after stopping the infusion and, in some instances, administering medications and/or IV fluids.

Thus, generalized IRR is a risk following the repeated administration of ATYR1940. In an effort to mitigate this risk, the infusion duration and volume of infusion have been increased. These changes are intended to decrease the concentration of ATYR1940 being infused at any given time and allow for medical assessment earlier in the course of an IRR by providing a wider window to stop the infusion before the entire dose has been administered.

In addition, patients are to be closely monitored for a generalized IRR throughout the study drug infusion. Signs and symptoms of a generalized IRR may vary among patients, and may include, but are not limited to, one or more of the following:

- Fever
- Chills, rigors, myalgia
- Facial or systemic erythema, pallor, facial swelling

- Chest tightness, difficulty breathing, wheezing, stridor, tachypnea, bronchospasm, cough
- Tachycardia or significant pulse rate increase from baseline without other obvious cause
- Bradycardia or significant pulse rate decrease from baseline
- Pre-syncope or syncope
- Hypotension, orthostatic hypotension, or blood pressure swings, including hypertension
- Skin rash, urticaria, angioedema, or pruritus
- Swelling of the throat, tongue, mouth, or lip
- Difficulty speaking; hoarse or raspy voice
- Excessive salivation; difficulty swallowing
- Nausea, vomiting, cramps, or diarrhea
- Development of a headache, especially moderate or greater, after start of infusion

A generalized IRR could be occurring when any symptoms suggestive of such a reaction 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.

In the event of a generalized IRR, study drug infusion must be stopped immediately (and not re-administered) and appropriate medical care must be given. 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 per Section 8.5.9.4.

7.5.5.2. Jo-1 Antibody Testing, Stopping Rules, and Anti-Synthetase Syndrome

In patients treated with ATYR1940 who experienced a generalized IRR, low levels of an antibody known as Jo-1 Ab have been detected. These antibodies are directed against ATYR1940 (and the parent protein, HARS). The nature of the relationship of these antibodies to the generalized IRRs is not yet clear, but the development of either Jo-1 Ab levels and generalized IRRs or both has been identified as a risk following the repeated administration of ATYR1940. These risks, however, can be monitored closely, including by assessment of Jo-1 Ab levels using a commercial assay and monitoring for signs of generalized IRRs. Because generalized IRRs have occurred in association with low levels of Jo-1 Abs, a low threshold of Jo-1 Abs has been set: patients who develop Jo-1 Ab levels of ≥1.5 U/mL will discontinue ATYR1940, but continue to be followed as

described in this section, and patients with Jo-1 Ab levels ≥1.5 U/mL will be excluded from study participation.

A very rare autoimmune disorder known as anti-synthetase syndrome, characterized clinically by an inflammatory myopathy, skin manifestations, arthritis, and often associated with interstitial lung disease,[47,48] is associated with Jo-1 Ab as well, albeit at higher Jo-1 Ab levels than observed during ATYR1940 dosing. The pathophysiological processes that lead to the development of this rare syndrome, and to auto-immune responses to HARS, are not known. Clinical and genetic factors, including human leukocyte antigen haplotype, that confer increased risk for the development of anti-synthetase syndrome have been identified, but how these factors confer risk is poorly understood.[49]

The diagnosis of an anti-synthetase syndrome is made based on a combination of clinical findings and Jo-1 Ab levels through commercially available serological assessments.[50] Anti-synthetase syndrome, once diagnosed, is usually treated by immunosuppression, often by the use of systemic corticosteroids.[48]

The development of an anti-synthetase syndrome is a theoretical, albeit unlikely risk following the repeated administration of ATYR1940. This risk, however, can be monitored closely, by assessment of clinical signs and symptoms and by following Jo-1 Ab levels. With the commercial Jo-Ab assay used in this study, a level of 7 U/mL is thought to be the lower limit for an equivocal finding of Jo-1 Ab-associated anti-synthetase syndrome and a level of 10 U/mL is considered positive. The risk of a patient developing Jo-1 Ab levels diagnostic for anti-synthetase syndrome is mitigated by the fact that ATYR1940 dosing will be discontinued if a Jo-1 Ab level of ≥1.5 U/mL is reached.

The actions listed below are to be taken by the Investigator to manage patients with a Jo-1 Ab result that reaches the threshold of ≥1.5 U/mL during the study.

1) The patient will no longer receive ATYR1940, *and*
2) The patient will return to the study center for visits as per protocol, if feasible, and be required to return to the clinical site for the 1-, 4-, and 12-week posttreatment follow-up visits, at a minimum.

In addition, any patient who develops clinical manifestations of an anti-synthetase syndrome (with or without reaching a Jo-1 Ab threshold of ≥1.5 U/mL) will:

1) No longer receive ATYR1940, if the clinical manifestations occur before administration of any planned dose, *and*
2) Receive appropriate, acute medical treatment as warranted clinically, including immunosuppressive interventions, *and*
3) Be referred to an appropriate medical professional (e.g., rheumatologist or equivalent) who is experienced with anti-synthetase syndrome, *and*
4) Return to the study center for visits as per the protocol schedule, if feasible, but must attend the 1-, 4-, and 12-week posttreatment follow-up visits, at a minimum.

The Medical Monitor will monitor patients' Jo-1 Ab levels concurrently with the Investigator during the conduct of the study, and will confer regarding any patient(s) with rising Jo-1 Ab titers. The Medical Monitor and Investigator will discontinue ATYR1940 for patients whose Jo-1 Ab level reaches ≥1.5 U/mL. The Investigator must inform the study Medical Monitor promptly regarding any patient who develops clinical manifestations of an anti-synthetase syndrome.

Patients in whom sufficiently high Jo-1 Ab levels develop will have samples tested for Ab isotyping (immunoglobulin G/immunoglobulin M). The neutralizing capacity of the Ab may be tested as well.

7.5.5.3. Anti-Drug Antibodies

The development of humoral immune responses characterized by the formation of Ab to exogenously administered proteins occurs commonly. ATYR1940 is a protein-based therapeutic, a truncated version of the human protein, HARS, which is 100% identical to the wild-type human sequence. ADAs were observed following single-dose administration of ATYR1940 in nonclinical studies and when administered to healthy subjects. The ADAs in humans occurred infrequently, titers were low, and the development of an ADA response was neither associated with any safety laboratory abnormalities nor temporal adverse systemic clinical symptoms. These clinical data suggest that ADAs may be observed in the current clinical study. The Sponsor has developed a sensitive assay to detect ADAs to ATYR1940, which will be utilized in this study. Specifically, all patients will have repeated ADA assessments during the study

(see Table 1), to monitor the presence or absence of ADAs, and measure titers, where present.

For patients with elevated ADA at the 12-week F/U visit, additional ADA testing should be performed every 1 to 3 months until the level returns to the pre-infusion baseline.

Patients in whom sufficiently high titer ADAs develop will have samples tested for immunoglobulin G and M against ATYR1940 as well as ADA neutralizing capacity.

7.5.5.4. Clinical Monitoring

The development of clinically significant immunogenicity, including immediate hypersensitivity reactions, delayed hypersensitivity reactions, and immune complex deposition, is a potential safety concern for any biological drug candidate. This study includes specific safety measures to monitor for this risk, and prospectively manage any potential adverse effects. Clinical monitoring includes close observation for generalized IRRs during, or shortly after, IV infusions of ATYR1940, including vital signs, ECGs, pulse oximetry, and PFTs. Frequent physical examinations with vital signs will be conducted during the course of the study to monitor for symptoms of potential generalized IRRs (see Section 7.5.5.1). Safety laboratory examinations will be performed at each visit, including serum chemistry evaluations and complete blood counts. Blood samples to assess for signs of immunogenicity will be taken periodically (Table 1).

Infusion of ATYR1940 will be discontinued in any patient who has symptoms of a generalized IRR (see Section 7.5.5.1). Patients with evidence of a generalized IRR should have additional procedures and tests performed as outlined in Section 8.5.9.4.

7.5.6. Data Monitoring Board

A Data Monitoring Board (DMB), consisting of at least 4 independent physicians and a statistician with expertise in clinical research, clinical immunology, and the clinical management of muscular dystrophies, has been assembled to review safety data and other pertinent data from all ongoing clinical studies of ATYR1940. The ATYR1940 DMB will meet on a quarterly basis to review available, interim clinical safety and other pertinent data as defined for each protocol, from all patients enrolled in studies of ATYR1940, including this study.

7.6. Rationale for the Dose(s) Selected

For the first 12 weeks in this extension study, patients will receive ATYR1940 at the highest tolerated dose received in the parent study; no dose adjustments are allowed during this 12-week period. After 12 weeks, if the patient is demonstrating good tolerability, the ATYR1940 dose may be increased on a patient-specific basis at the Investigator's discretion, in consultation with the Sponsor and Medical Monitor. ATYR1940 dose increases to >3.0 mg/kg are not permissible.

7.7. Prior and Concomitant Medications and Procedures

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

- Immunomodulatory agents, as follows:
  - Targeted biological therapies (e.g., etanercept, omalizumab) are prohibited during study participation.
  - Corticosteroids are prohibited during study participation.
  - Non-steroidal anti-inflammatory drugs (NSAIDS): High-dose NSAIDs (either stable or intermittent dosing) are prohibited during study participation. Contact the Medical Monitor if questions arise regarding the definition of high-dose.
    - Low-dose NSAIDs (stable daily dosing) are acceptable during the study and should be maintained through the last scheduled MRI.
    - Low-dose NSAIDs (intermittent dosing in patients not on stable dose) are permitted to treat pain during the study, with the exception of within 48 hours before each MRI.
- Vaccination during study participation is prohibited.
- All investigational agents or devices (other than ATYR1940 and mobility devices) are prohibited during study participation.
- Products that putatively enhance muscle growth (e.g., insulin-like growth factor, growth hormone) or activity (e.g., Coenzyme Q, Coenzyme A, creatine, L-carnitine) are prohibited during study participation.
- Curcumin is prohibited during study participation.
- Systemic albuterol is prohibited during study participation. (Intermittent inhaled albuterol is permissible.)
- Initiation of statins (as a new drug to a patient) or significant adjustment to statin regimen is prohibited during the study. Stable, chronic statin use is permissible.
- Major surgeries are prohibited during study participation.
- Muscle biopsies involving muscles being followed in the current study are prohibited during study participation.

The Investigator should contact the Medical Monitor with any questions or clarifications regarding concomitant medications.

All other concomitant medications and procedures are allowed.

All medications, including vitamin and anti-oxidant supplements, are to be recorded in the source documents and in the eCRF.

8. STUDY VISITS AND ASSESSMENTS

8.1. Informed Consent and, if applicable, Assent

All patients must provide written informed consent or assent, as appropriate, 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. Assent to participate, along with parental/guardian written informed consent, is required for patients who are not age of majority at the time of screening and/or enrollment, according to IEC/EC requirements. Patients who become of majority age during the course of the study are required to provide written informed consent to continue participation.

8.2. Pregnancy Testing

Urine β-human chorionic gonadotropin pregnancy testing is to be performed for female patients of childbearing potential (i.e., premenopausal or not surgically sterile) before ATYR1940 infusion at Week 1. Any patient with a positive result is not eligible for study participation. Urine pregnancy testing also is to be performed during the study at the time points indicated in Table 1. All samples will be analyzed by the local laboratory. Study drug is to be discontinued for any patient determined to be pregnant during study participation (see Section 6.4.1 and 8.5.10.8).

8.3. Concomitant Medications

All medications and supplements the patient received after completion of the last visit in the parent study and 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.

8.4. Pharmacodynamic and Pharmacokinetic Measurements

8.4.1. Pharmacodynamics

8.4.1.1. Muscle Biomarker Panel

Blood samples for the assessment of serum-based muscle biomarkers will be collected from all patients at the time points indicated in Table 1.

8.4.1.2. Muscle Surveillance Magnetic Resonance Imaging

MRI is a non-invasive method that can be applied to the study of skeletal muscle tissue, not only for assessment of anatomy and structure, but also to assess aspects of muscle pathophysiology, including inflammation and fatty infiltration[41,51,52] in muscular dystrophy patients. MRI will be performed in this study to evaluate changes in lower extremity muscle disease burden following treatment with ATYR1940, based on changes in inflammation within skeletal muscle tissue.

Patients without contraindications for MRI (e.g., metal prosthesis or pacemaker, per site MRI protocol, as well as those with disease features precluding ability to perform MRI) will undergo a lower extremity skeletal muscle Surveillance MRI examination at the time

points designated in Table 1. Imaging will be performed locally at each site, using either 1.5 or 3.0 Tesla Siemens or Philips scanner, based on a protocol provided in the Imaging Acquisition Protocol. The MRI scans will be formatted to acquire multiple acquisition sequences, including T1 and STIR.

Images will be reviewed and interpreted by a central reader with expertise in muscle MRI, as outlined in the Imaging Acquisition Protocol. For each time point, muscle inflammation will be assessed based on the presence or absence of STIR hyperintensity, and fat infiltration on T1-weighted sequences will be graded using the Fischer score.Wattjes, Kley, Fischer [53]

8.4.1.3. Manual Muscle Testing

Muscle strength is to be formally assessed at the time points designated in Table 1 by the Investigator or designee using consistent methodology and by the same individual at the study center at all scheduled visits, if feasible.

Muscles are to be tested in the order defined in Table 2. Generally, for bilateral muscle testing, each muscle group is first tested on the right and then the left, prior to proceeding to the next muscle group. Some muscle groups are listed with anti-gravity testing, but for a weaker patient, these are to be tested in a side-lying or supine position, per Table 3; the re-test for a weaker patient is indicated in italics. The ankle plantar flexors are first tested in prone, and then retested in standing for scoring purposes. Results will be graded using a modified Medical Research Council scale[54] (see Table 4).

Table 2: Manual Muscle Testing Order

Position / Muscle Group	Order of Testing
Sitting	
Trapezius (shoulder elevators)	1
Deltoid middle (shoulder abductors)	2
Biceps brachii (elbow flexors)	3
Wrist extensors (extensor carpi ulnaris/radialis)	4
Wrist flexors (flexor carpi radialis/ulnaris)	5
Iliopsoas (hip flexors)	6
Quadriceps femoris (knee extensors)	7
Ankle dorsiflexors (tibialis anterior)	8
Supine	
Neck flexors (scalenes, sternocleidomastoid)	9
Trapezius (gravity eliminated test if needed) -	
Deltoid middle (gravity eliminated test if needed) -	
Gluteus medius (gravity eliminated test if needed) -	

Sidelying (lying on left side-right muscles tested)	
Gluteus medius (hip abductors)	10
Iliopsoas (gravity eliminated test if needed) -	
Gluteus maximus (gravity eliminated test if needed) -	
Hamstrings (gravity eliminated test if needed) -	
Biceps brachii (gravity eliminated test if needed) -	
Neck flexors (gravity eliminated test if needed) -	
Neck extensors (gravity eliminated test if needed) -	
Prone	
Neck extensors (longissimus, semispinalis, iliocostalis, splenius cervicis)	11
Gluteus maximus (hip extensors)	12
Hamstrings (knee flexors)	13
Ankle plantar flexors (initial test; gastrocnemius)	14
Sidelying (lying on right side-left muscles tested)	
Gluteus medius (hip abductors)	15
Iliopsoas (gravity eliminated test if needed) -	
Quadriceps (gravity eliminated test if needed) -	
Gluteus maximus (gravity eliminated test if needed) -	
Hamstrings (gravity eliminated test if needed) -	
Biceps brachii (gravity eliminated test if needed) -	
Ankle dorsiflexors (gravity eliminated test if needed) -	
Standing	
Ankle plantar flexors (second test if needed)	16

Table 3: Manual Muscle Testing Positions

	Testing Positions	
Muscle Group	**Anti-gravity**	**Gravity Eliminated**
Trapezius (shoulder elevators)	Sitting	Supine
Deltoid middle (shoulder abductors)	Sitting	Supine
Biceps brachii (elbow flexors)	Sitting	Sidelying
Wrist extensors Sitting (pronation)	Sitting (pronation)	Sitting (neutral)
Wrist flexors Sitting (supination)	Sitting (supination)	Sitting (neutral)
Iliopsoas (hip flexors)	Sitting	Sidelying
Quadriceps femoris (knee extensors)	Sitting	Sidelying
Ankle dorsiflexors	Sitting	Sidelying
Neck flexors	Supine	Sidelying
Gluteus medius (hip abductors)	Sidelying	Supine
Neck extensors	Prone	Sidelying
Gluteus maximus (hip extensors)	Prone	Sidelying
Hamstrings (knee flexors)	Prone	Sidelying
Ankle plantar flexors	Prone/Standing	Sidelying

Table 4: Manual Muscle Testing Grading Scale

Description	Grade
Normal strength	5
Uncertain muscle weakness	5-
Inability to resist against maximal pressure throughout range of motion	4+
Ability to resist against moderate pressure throughout range of motion	4
Ability to resist against minimal pressure throughout range of motion	4-
Ability to move through full range of motion against gravity and to resist against minimal pressure through partial range of motion, then contraction breaks abruptly	3+
Ability to move through full range of motion against gravity	3
Ability to move through greater than one half range of motion against gravity	3-
Ability to move through less than one half range of motion against gravity	2+
Ability to move through full range of motion with gravity eliminated	2
Ability to move in any arc of motion with gravity eliminated	2-
A flicker of movement is seen or felt in the muscle	1
No contraction palpable	0

Extracted from Personius KE et al. Physical Therapy. 1994;74:253-263. Available from http://ptjournal.apta.org/content/74/3/253.full.pdf.

8.4.1.4. Functional Assessment of Upper and Lower Limbs

Upper extremity muscle function will be measured using the Brooke scale (see Table 5). Lower extremity muscle function will be measured using the Vignos scale (see Table 6). These scales are commonly used in studies of neuromuscular disorders.[55] Lower scores on each of these scales are associated with better muscle function.

Grades of both upper and lower extremity muscle function will be based on the Investigator's (or designee's) commands and/or direct observation of patient ability to perform the movements or activities specified.

Table 5: Grading System for the Brooke Scale

Grade	Description
1	Starting with arms at the sides, the patient can abduct the arms in a full circle until they touch above the head
2	Can raise arms above head only by flexing the elbow (shortening the circumference of the movement) or using accessory muscles
3	Cannot raise hands above head, but can raise an 8-oz glass of water to the mouth
4	Can raise hands to the mouth, but cannot raise an 8-oz glass of water to the mouth
5	Cannot raise hands to the mouth, but can use hands to hold a pen or pick up pennies from the table
6	Cannot raise hands to the mouth and has no useful function of hands

Extracted from: Lu Y-M, Lue Y-J. Strength and Functional Measurement for Patients with Muscular Dystrophy. In: Hegde M, ed. Muscular Dystrophy, 2012. ISBN: 978-953-51-0603-6, InTech. Available from: http://www.intechopen.com/books/muscular-dystrophy/strength-decrease-pattern-and-functional-measurement-for-patients-with-muscular-dystrophy.

Table 6: Grading System for the Vignos Scale

Grade	Description
1	Walks and climbs stairs without assistance
2	Walks and climbs stair with aid of railing
3	Walks and climbs stairs slowly with aid of railing (over 25 seconds for eight standard steps)
4	Walks unassisted and rises from chair but cannot climb stairs
5	Walks unassisted but cannot rise from chair or climb stairs
6	Walks only with assistance or walks independently with long leg braces
7	Walks in long leg braces but requires assistance for balance
8	Stands in long leg braces but unable to walk even with assistance
9	Is in a wheelchair
10	Is confined to a bed

Extracted from: Lu Y-M, Lue Y-J. Strength and Functional Measurement for Patients with Muscular Dystrophy. In: Hegde M, ed. Muscular Dystrophy, 2012. ISBN: 978-953-51-0603-6, InTech. Available from: http://www.intechopen.com/books/muscular-dystrophy/strength-decrease-pattern-and-functional-measurement-for-patients-with-muscular-dystrophy.

8.4.1.5. INQoL

The INQoL is a validated, muscle-disease-specific measure of quality of life. The self-administered questionnaire consists of 45 questions within 10 sections. Four sections focus on the impact of key muscle disease symptoms (weakness, locking [i.e., myotonia], pain, and fatigue); 5 sections focus on the impact (degree and importance of impact) muscle disease has on particular areas of life; and the remaining section focuses on the

positive and negative effects of treatment.[56] Patients will complete the InQoL at the time points designated in Table 1.

8.4.1.6. FSHD-specific Health Inventory

The FSHD-HI is a validated, disease-specific patient outcome measure for FSHD that measures a patient's perception of their total disease burden and 14 additional areas of FSHD symptomatic health.[57] The FSHD-HI consists of 116 questions and takes approximately 15 minutes to complete.

Patients will complete the FSHD-HI at the time points designated in Table 1. The FSHD-HI should be completed at the same time of day and before other assessments scheduled for that day, including the InQoL. The order of assessments should remain consistent throughout the study.

8.4.1.7. Biomarkers

Nonclinical studies suggest ATYR1940 may have an immunomodulatory impact on myopathies with an immune component, such as LGMD2B and FSHD. Such activity will be examined in this study by measuring circulating biomarkers, immunophenotyping of PBMCs, and measuring the release of cytokines from PBMCs *ex vivo*, all of which have been reported previously to be dysregulated in patients with FSHD. Blood samples for assessment of biomarkers, immunophenotyping in PBMCs, and *ex vivo* culturing for disease-related immune protein release in PBMCs will be collected before, during, and following treatment with ATYR1940, at time points specified in Table 1.

All biomarkers will be analyzed by designated central laboratories. Biomarkers to be measured may include, but are not limited to, those listed in Table 7.

Table 7: Biomarkers to be Measured in Blood

Biomarkers
GM-CSF, IFN-γ, IL-10, IL-18, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, MIP-1-α, MIP-1-β, MCP-1, TNF-α, TNF-β
BDNF, Eotaxin-1, Factor VII, ICAM-1, IL-1-α, IL-1-β, IL-1ra, IL-12p40, IL-12p70, IL-15, IL-17, IL-23, MMP-3, MMP-9, SCF, VEGF
AAT, C3, Fibrinogen, Haptoglobin, IgA, IgM, VDBP
CD40, CD40-L, G-CSF
E-Selectin, IP-10, IL-6r, MIP-3 alpha, MCP-2, MCP-4, MIG, MPIF-1
ENA-78, IL-13, IL-16, MDC, CK-MB, IgE, PSA-f
Amphiregulin, Epiregulin, FGFb, HB-EGF, PLGF, PDGF-BB, Tenscin C, TGFa, EGF, EGFr
B2M, Lp(a), CRP, SAP, SHBG, TBG, vWF, Vitronectin
EPO, MPO

Note: Biomarkers are defined in the Laboratory Manual.

For all analytes, the date and actual time of sample collection will be recorded in the source documents and the eCRF. Refer to the Laboratory Manual for details regarding sample processing, storage, and shipment.

8.4.2. Pharmacokinetics

Formal PK will not be determined as a part of this study; however, systemic exposure to ATYR1940 will be confirmed. Serum concentrations of ATYR1940 will be determined from samples collected at end of infusion and 4 hours after the start of infusion at the time points designated in Table 1.

The date and actual time of sample collection will be recorded in the source documents and the eCRF.

Samples will be analyzed by a central laboratory. Refer to the Laboratory Manual for details regarding sample processing, storage, and shipment.

8.5. Safety Measurements

8.5.1. Physical Examination, including Neurological Examinations

Complete physical examinations are to be performed at the time points indicated in Table 1. The complete physical examination includes assessment of the following:

- General appearance
- Head, eyes, ears, nose, and throat
- Cardiovascular system
- Respiratory system
- Gastrointestinal system (abdomen)
- Lymphatic system
- Musculoskeletal system
- Skin
- Psychiatric
- Neurological - A complete neurologic examination, including assessment of mental status, memory, cranial nerves, motor function, reflexes, and sensory testing, is to be performed as part of the complete physical examination.

Physical examinations may also be performed at any time during the study, as clinically indicated.

Abnormal, clinically significant examination findings are to be reported as an AE, if the finding represents a change from baseline.

8.5.2. Weight

Body weight is to be measured at the time points designated in Table 1, as well as prior to dosing any time the Investigator suspects the patient has experienced a notable change in weight (± 10%).

The patient's Week 1 weight (from the current study) is to be used to calculate the ATYR1940 dose. If the patient has experienced a notable change in weight, as defined above, the Medical Monitor is to be notified regarding recalculation of ATYR1940 dose. Any change in total ATYR1940 dose resulting from a change in body weight is to be documented in the source documents and in the eCRF.

8.5.3. Visual Acuity (Patients who Participated in Parent Study ATYR1940-C-003 Only)

Standardized best corrected visual acuity for the right and left eyes will be documented and recorded in the eCRF at the time points indicated in Table 1. The method used to evaluate visual acuity in the parent study should be continued for each patient for consistency.

8.5.4. Pure Tone Audiometry (Patients who Participated in Parent Study ATYR1940-C-003 Only)

Pure tone audiometry will be performed for right and left ears by an audiometrist and will be documented and recorded in the eCRF at the time points indicated in Table 1.

8.5.5. Vital Signs

Vital signs are to be measured prior to any scheduled blood sample collection. On dosing days, vital signs are to be measured pre-infusion; every 30 minutes (±5 minutes) during the infusion; and at the end of the infusion (±5 minutes); at 30 minutes (±5 minutes) after the end of infusion; and at additional time points as clinically indicated. Both preinfusion and postinfusion vital signs will be measured before any scheduled blood sample collection.

Abnormal, clinically significant vital signs results are to be reported as AEs, if the finding represents a change from baseline.

Additional vital signs are required for patients with evidence of a generalized IRR, as described in Section 8.5.9.4.

8.5.6. Pulse Oximetry

Pulse oximetry is to be performed from 5 minutes prior to infusion until 30 minutes (-5 minutes, +15 minutes) after the end of infusion at the time points indicated in Table 1 and as clinically indicated if the patient experiences pulmonary signs or symptoms (e.g., chest tightness, increased respiratory rate). Readings below 95% are to be noted.

Additional pulse oximetry is required for patients with evidence of a generalized IRR, as described in Section 8.5.9.4.

8.5.7. Pulmonary Function Tests

The following PFTs are to be measured at the time points indicated in Table 1. On study drug administration days, these PFTs are to be measured 2.5 hours (±30 minutes) after the end of infusion.

- Forced expiratory volume in 1 second (FEV_1)
- Forced vital capacity (FVC)
- FEV_1/FVC ratio

The following PFTs also are to be measured at the time points indicated in Table 1:

- Total lung capacity
- Diffusion capacity of the lung for carbon monoxide (DLCO)

Patients for whom a facial mask was used for PFT assessments in the parent study should continue to use a facial mask for all PFT assessments in this study.

Additional PFTs are required for patients with evidence of a generalized IRR, as described in Section 8.5.9.4.

8.5.8. 12-Lead Electrocardiogram

A 12-lead ECG is to be performed at the time points indicated in Table 1. On study drug administration days, 12-lead ECGs are to be performed prior to and 30 minutes (±15 minutes) following the end of infusion and reviewed by the Investigator.

Heart rate; PR, QR, and QT (uncorrected) intervals will be recorded on the eCRF.

Abnormal, clinically significant ECG results are to be reported as AEs, if the finding represents a change from baseline.

Additional ECGs are required for patients with evidence of a generalized IRR, as described in Section 8.5.9.4.

8.5.9. Safety Laboratory Tests

8.5.9.1. Hematology, Serum Chemistries, and Urine Analysis with Microscopy

Blood samples are to be collected for assessment of hematology and serum chemistry parameters and urine samples for urine analysis with microscopy, at the time points indicated in Table 1. Laboratory samples are to be collected after vital signs are measured.

Samples will be analyzed by the central laboratory.

The following safety laboratory parameters will be measured:

Hematology

- Hematocrit
- Hemoglobin
- Red blood cell (RBC) count
- White blood cell (WBC) count
- Platelet count
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Serum Chemistries

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Total bilirubin
- Insulin-like growth factor 1
- Gamma-glutamyl transferase
- Alkaline phosphatase
- Blood urea nitrogen
- Creatinine
- Lactate dehydrogenase
- Creatine kinase (CK)*
- Troponin
- Myoglobin
- C-reactive protein
- Total protein
- Cholesterol (non-fasting)
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Magnesium
- Calcium
- Inorganic phosphate

Urine Analysis and Microscopy

- Color
- Specific gravity
- Glucose
- Blood
- pH
- Protein
- Ketones
- Microscopy (including RBCs, WBCs, RBC casts, WBC casts, bacteria, and crystals)

*Elevated CK values will be fractionated.

Safety laboratory tests may be repeated as necessary during treatment at a schedule determined by the Investigator, based on the patient's clinical status.

Abnormal, clinically significant laboratory findings observed are to be reported as AEs, if the finding represents a change from baseline.

Additional safety laboratory tests are required for patients with evidence generalized IRR, as described in Section 8.5.9.4.

8.5.9.2. Complement and Tryptase

Blood samples for measurement of C3a, C4a, C5a, Bb, and SC5b-9 in plasma and CH50, C3, C4 and tryptase in serum are to be collected according to the schedule defined in Table 1. A central laboratory will be used for sample analysis. Other products of complement may be tested as appropriate.

8.5.9.3. Antibody and HARS Measurements

Blood samples for measurement of Jo-1 Ab, ADA, and serum HARS levels are to be collected according to the schedule defined in Table 1. Samples will be analyzed by a central laboratory. The Week 1 Jo-1 Ab sample must be obtained and result reviewed within 2 weeks prior to the first ATYR1940 dose.

For patients with elevated ADA at the 12-week F/U visit, additional ADA testing should be performed every 1 to 3 months until the level returns to the pre-infusion baseline.

8.5.9.4. Additional Laboratory Testing and Procedures in Patients with Generalized Infusion-Related Reactions

Patients who experience generalized IRRs (see Section 7.5.5.1) must have their infusion stopped and be treated as medically indicated. Vital signs, pulse oximetry, and ECGs are to be performed to gather clinical information as soon as possible after the onset of clinical symptoms of a generalized IRR (for instance, immediately after cessation of the study drug infusion if such a reaction is seen). Vital signs are to be monitored as medically indicated and pulse oximetry is to be monitored continuously for at least 2 hours after the end of infusion 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, and SC5b-9)
- Serum complement (CH50, C3, and C4) and tryptase

Additionally, the following tests and procedures are to be performed 1.5 to 2 hours after the onset of symptoms:

- Samples for assessment of:
  - Complete safety laboratory panel, including urine analysis and microscopy (Section 8.5.9.1)
  - Plasma complement factors (C3a, C4a, C5a, Bb, and SC5b-9)
  - Serum complement (CH50, C3, and C4) and tryptase
  - Biomarkers and ATYR concentrations
- PFTs – FEV_1, FVC, FEV_1/FVC ratio, total lung capacity, DLCO

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.

8.5.10. Adverse Events

8.5.10.1. Definitions

8.5.10.1.1. Adverse Event

An AE is defined in the ICH Guideline for Good Clinical Practice 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, (i.e., 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 (i.e., 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." Classification of AEs is to be done by the Investigator is according to the NCI CTCAE, version 4.03.

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.

8.5.10.1.2. 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.

8.5.10.1.3. 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 (i.e., places the patient at immediate risk of death)
- requires in-patient hospitalization 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 stay in a health care facility. Any AE that does not meet one of the definitions of serious (i.e., 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.

8.5.10.1.4. 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 severity that has been 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.

8.5.10.1.5. Serious and Unexpected Suspected Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is any event that meets all 3 of the following definitions:

1) suspected adverse reaction (Section 8.5.10.1.2);

2) serious (Section 8.5.10.1.3); and

3) unexpected (Section 8.5.10.1.4).

8.5.10.2. Adverse Event Assessment

All AEs will be collected and recorded in this study from the time of the first ATYR1940 dose in this study through the EOS visit, or after the end of the study, if thought to be related to study drug. (AEs occurring through 30 days after the last study drug dose in the parent study and those occurring >30 days after the last study drug dose in the parent study that are considered by the Investigator to be study drug-related are to be reported in the parent study.) This includes AEs the patient reports spontaneously, those observed by the Investigator, and those elicited by the Investigator in response to open-ended questions during scheduled study center visits. Furthermore, all AEs that presented in the parent study that are ongoing at Week 1 in the current study will be recorded as such.

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 8.5.10.1.3 are to be considered serious.

Relationship to Study Drug

The relationship of each AE to ATYR1940 is to be assessed by the Investigator according to categories in Table 8.

Table 8: Criteria for Determination of Adverse Event Relationship to Study Drug

Relationship between ATYR1940 and AE:					
	Category				
AE (is):	**None**	**Unlikely**	**Possibly**	**Likely**	**Definitely**
Clearly the result of an external factor	Yes	No	No	No	No
Probably/possibly the result of another factor	No	Yes	Yes	No	No
Has a chronological relationship with the time of administration and/or represents a known reaction to Study Drug	No	No	Yes	Yes	Yes
Disappears or decreases after discontinuation of the Study Drug	NA	NA	NA	Yes	Yes
Recurs on renewed administration (re-challenge)	No	No	NA	NA	Yes or NA**

** A re-challenge is not required; if done, re-challenge would be expected to be positive.

NA Not applicable

Intensity

The intensity of each AE is to be assessed by the Investigator according to the NCI CTCAE, version 4.03. If the AE is not included in the NCI CTCAE, version 4.03, then the Investigator is to determine the intensity of the AE according to the following criteria:

- 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.
- Death (Grade 5) related to an AE.

8.5.10.3. Recording Adverse Events

All AEs occurring from the time written informed consent is obtained through the EOS visit 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 ATYR1940, ATYR1940 action taken, outcome, and whether the event is classified as serious.

8.5.10.4. Reporting Serious Adverse Events

SAEs will be collected and recorded throughout the study period, beginning with the signing of the ICF through the EOS visit, or after the end of the study if thought to be related to ATYR1940.

The Investigator must report all SAEs within 24 hours of discovery to:

[redacted]

Email: [redacted]

Telephone number: [redacted]

A completed SAE report is to be sent to the Medical Monitor's attention within 24 hours of discovering the event. 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 ATYR1940.

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

The Investigator, or designated party, should notify the appropriate IRB/EC 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 possible or probably related to the investigational product, and as unexpected (i.e., SUSARs), will be reported to the concerned Competent Authorities (CAs) and IRBs/ECs 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 CAs/IRBs/ECs within 7 calendar days, and additional information within an additional 8 calendar days. The Sponsor or Sponsor[1]s designee is required to submit any other SUSAR to the CAs/IRBs/ECs within 15 calendar days of notification. The Sponsor or its designee is also responsible for notifying the investigational sites of all expedited SAEs. The Investigator must keep copies of all expedited SAE information including correspondence with the Sponsor on file.

8.5.10.5. Follow-Up of Adverse Events

The Investigator must continue to follow all SAEs and non-serious AEs considered to be at least possibly related to ATYR1940 either until resolution or the Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

8.5.10.6. Reporting Safety Information

The Investigator must promptly report to his or her IRB/EC all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs reasonably or possibly associated with the use of ATYR1940 according to the IRB/EC's procedures.

The Sponsor will assess the severity and frequency of adverse drug reactions in adults versus pediatric patients, and will submit findings annually in the Development Safety Update Report/Annual Report.

8.5.10.7. Protocol Deviations Due to an Emergency or Adverse Event

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

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

8.5.10.8. Pregnancy

Pregnancies occurring while the patient is receiving ATYR1940 or within 30 days after the patient's last dose of ATYR1940 will not be considered serious, but are to be reported using the same procedures as for SAEs described in Section 8.5.10.4.

ATYR1940 must be discontinued immediately 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 (i.e., 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 ATYR1940 should also be reported.

9. STATISTICAL ANALYSES

9.1. Statistical Basis for Sample Size

No formal sample size calculation was performed; patients that participated in the parent study and meet the entry criteria for the current study may be enrolled. Based on the design of the parent studies, it is estimated that up to 24 patients will be enrolled in this study.

9.2. Statistical and Analytical Plan

An overview of the statistical methodology to be employed is provided in the following subsections. Details regarding the statistical methodology will be documented in a formal Statistical Analysis Plan (SAP) prior to database lock. The methodology for serum ATYR1940 concentrations and PD analyses will be documented in separate SAPs.

9.2.1. General Methods

Statistical analyses will be primarily descriptive in nature, since the goal of the study is to determine the safety, tolerability, and immunogenicity of ATYR1940. This goal will be achieved by the results of a deterministic algorithm; thus, statistical hypothesis testing is neither intended nor appropriate within this context.

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.

Data obtained from the parent study will be combined with data from the current study.

For patients assigned to ATYR1940 in the parent study, data obtained from the parent study will be combined with data from the current study.

For patients who received ATYR1940 ≤4 weeks previously in the parent study, baseline refers to the baseline in the parent study (i.e., the most recent assessment obtained before the first study drug dose.) For patients who received ATYR1940 >4 weeks previously in the parent study, baseline refers to assessment obtained before the first ATYR1940 dose at Week 1 in the current study.

9.2.2. Analysis Populations

All patients who have received at least 1 dose (partial or full) of ATYR1940 and have a postinfusion safety observation will be included in safety analyses. Additional analysis populations will be defined in the SAP.

9.2.3. Missing, Unused, and Spurious Data

Analyses will be based on observed data only; no data will be imputed.

9.2.4. Disposition of Patients

The numbers and proportions of patients who are enrolled in and complete the study and who are early terminations will be summarized. Reasons for study discontinuation after the start of study treatment will be tabulated.

9.2.5. Demographics and Baseline Characteristics

A summarization of demographic and baseline disease characteristic data, as documented in each parent study, will be presented for patients in this extension study. Data to be tabulated will include at least demographic and baseline characteristics such as sex, age, race, height, weight, and body mass index, and disease-specific diagnostic and historical information. Medical history also will be similarly summarized.

9.2.6. Extent of Exposure

Descriptive statistics will be presented overall and, if applicable, each dose level, for the number of doses received, percent of expected dose received, and actual dose received overall (i.e., across the parent and extension study), and in each the parent and extension study. Furthermore, descriptive statistics for the number of doses missed or held will be presented, if warranted by the data. A tabular summary and listing of drug administration and dose intensity and a by-patient listing of the date and time of each ATYR1940 dose and the dose administered also will be presented.

9.2.7. Prior and Concomitant Medications

Tabulations of prior and concomitant medications, coded using the World Health Organization drug dictionary, will be produced. All prior and concomitant medications administered will be presented in a data listing.

9.2.8. Safety Analysis

9.2.9. Safety and Immunogenicity Analyses

Safety evaluations will be based on the incidence, type, and intensity of AEs, and changes from baseline in safety laboratory tests, ECG findings, vital signs measurements, PFTs, and pulse oximetry. Immunogenicity will be assessed based on the incidence of infusion site reactions, ADA titers, changes in Jo-1 and ADA titers over time, as appropriate, as well as changes from baseline over time in immune-based laboratory tests, including, for example, tryptase, complement factors, and cytokines. Safety variables will be tabulated and presented for all patients who receive any amount of study drug and have follow-up safety data. Tabulations will be presented for safety data overall and separately for the parent and extension studies.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization. The overall incidence of AEs occurring during the study will be summarized by MedDRA system organ class and preferred term. The incidence of TEAEs also will be summarized by system organ class

and preferred term. For the purpose of analysis, a TEAE is defined as any AE that occurs after administration of the first dose of ATYR1940 through the 12-week posttreatment follow-up visit, or any event that is present at baseline, but worsens in intensity or is subsequently considered drug-related by the Investigator. Severe TEAEs, SAEs, and discontinuation rates of study therapy due to TEAEs also will be summarized.

Events that are considered related to treatment (possibly, likely, or definitely drug-related) will also be tabulated. A tabulation will also be provided that enumerates TEAEs by maximum severity. Deaths, SAEs, and TEAEs resulting in study discontinuation will be tabulated, if warranted by the data.

All AEs occurring on study will be listed in by-patient data listings.

Clinical laboratory parameters will be summarized across time points and changes from baseline will be summarized. The frequency of clinically significant abnormal laboratory values will be tabulated. Shift tables will be produced for selected laboratory parameters, including at least hemoglobin, WBC count, absolute neutrophil count, absolute lymphocyte count, platelet count, AST, ALT, total bilirubin, alkaline phosphatase, creatinine, and electrolytes. These tables will summarize the number of patients with each baseline CTCAE grade and changes to the maximum CTCAE grade on study.

Changes in vital signs parameters (i.e., systolic and diastolic blood pressures, pulse rate, respiration rate, and body temperature) will be summarized across time points, and changes from baseline will be summarized. Changes in ECG findings, PFTs, and pulse oximetry will be summarized, as appropriate, and by-patient listings will be provided. Serological findings, including Jo-1 and ADA Ab titers will be tabulated, and by-patient listings provided.

Additional safety analyses may be determined at any time without prejudice, in order to enumerate rates of toxicities most clearly, and to define further the safety profile of ATYR1940.

9.2.10. Pharmacodynamic Analyses

9.2.10.1. Lower Extremity Skeletal Muscle MRI

Surveillance MRI of both of muscles in both of the lower extremities will be performed to assess muscle disease burden. At each time point, muscle inflammation will be assessed based on the presence or absence of STIR hyperintensity, and fat infiltration on T1-weighted sequences will be graded using the Fischer score.[53]

9.2.10.2. Biomarkers

Details regarding analyses of biomarkers will be the patient of a separate PK/PD analysis plan.

9.2.11. ATYR1940 Serum Concentrations

Details regarding serum concentrations of ATYR1940 and HARS levels will be covered under a separate PK/PD analysis plan.

9.2.12. Interim Analyses

Clinical data from this open-label study will be assessed at regular intervals during the conduct of the study. Safety data and other pertinent data will be summarized quarterly for review by the DMB (see Section 7.5.6).

9.3. Changes to the Planned Statistical Methods

Changes to the planned statistical methods will be documented in the clinical study report.

10. ETHICAL, LEGAL, AND ADMINISTRATIVE CONSIDERATIONS

10.1. 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.

10.2. Informed Consent

Written informed consent and assent, as appropriate, based on age of majority, in compliance with 21 Code of Federal Regulations § 50 and/or ICH and European regulations will be obtained from each patient prior to undergoing any protocol-specific tests or procedures that are not part of routine care.

aTyr or designee will provide informed consent form (ICF) and assent templates to the Investigator for use in developing a study center-specific consent documents. Prior to submission of the study center-specific ICF/assent form to the IRB/EC, these documents must be reviewed and approved by aTyr or designee. Any changes requested by the IRB/EC must also be approved by aTyr or designee. The final IRB/EC-approved ICF/ assent form must be provided to aTyr or designee. Revisions to the ICF/assent form required during the study must be approved by aTyr or designee, and a copy of the revised ICF/assent form provided to aTyr or designee.

Before recruitment and enrollment, each prospective patient (or legal guardian) will be given a full explanation of the study and be allowed to read the ICF/assent form in a language they understand. After the Investigator or designee is assured that the patient/legal guardian understands the commitments of participating in the study, the patient/legal guardian will be asked to sign and date the ICF and assent form, as appropriate.

A copy of the fully signed and dated ICF/assent form 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.

10.3. Institutional Review Board/Ethics Committee

Federal and European regulations and ICH require that approval be obtained from an IRB/EC prior to participation of patients in research studies. Approval by the Competent Authority, if applicable, or as required by local laws and regulations is also required in the EU. 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/EC.

All IRB/EC approvals must be dated and signed by the IRB/EC Chairperson or designee and must identify the IRB/EC 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/EC authorization has been received by aTyr 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/EC. The Investigator must supply aTyr 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/EC is constituted and operates in accordance with Federal and ICH GCP and any local regulations.

10.4. 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 aTyr or designee and the IRB/EC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB/EC for approval prior to patients being enrolled into the amended protocol.

aTyr may make administrative changes (i.e., 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.

10.5. Confidentiality

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 aTyr.

Patient confidentiality will be strictly maintained to the extent possible under the law. Patient names must not be disclosed. Patients will be identified in the eCRFs and other documents submitted to aTyr or its designated representative, by their initials, birth date, and/or assigned patient number. Documents that identify the patient (e.g., the signed ICF) should not to be submitted to aTyr or its designated representative, and must be maintained in confidence by the Investigator.

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

11. STUDY MANAGEMENT

11.1. Data Quality Assurance

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

11.2. 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.

aTyr or designee will provide eCRFs 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.

11.3. Monitoring

A CRA or other representative of the Sponsor will conduct a study center visit to verify the qualifications of each Investigator, inspect study center facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation

During the course of the study, the CRA will make study center 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.

11.4. Inspections

Regulatory authorities and/or quality assurance personnel from aTyr or its designated representative may wish to carry out such source data checks and/or in-center audit inspections. The Investigator assures aTyr 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.

11.5. 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.

11.6. 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.

12. REFERENCES

1. Mammen AL. Autoimmune myopathies: autoantibodies, phenotypes and pathogenesis. *Nature reviews. Neurology.* 2011;7(6):343-354.
2. Lundberg IE, Forbess CJ. Mortality in idiopathic inflammatory myopathies. *Clinical and experimental rheumatology.* 2008;26(5 Suppl 51):S109-114.
3. Pegoraro E, Hoffman EP. Limb-Girdle Muscular Dystrophy Overview. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews(R)*. Seattle (WA)1993.
4. Liu J, Aoki M, Illa I, et al. Dysferlin, a novel skeletal muscle gene, is mutated in Miyoshi myopathy and limb girdle muscular dystrophy. *Nature genetics.* 1998;20(1):31-36.
5. Mahmood OA, Jiang XM. Limb-girdle muscular dystrophies: where next after six decades from the first proposal (Review). *Molecular medicine reports.* 2014;9(5):1515-1532.
6. Nigro V, Savarese M. Genetic basis of limb-girdle muscular dystrophies: the 2014 update. *Acta myologica : myopathies and cardiomyopathies : official journal of the Mediterranean Society of Myology / edited by the Gaetano Conte Academy for the study of striated muscle diseases.* 2014;33(1):1-12.
7. Bansal D, Miyake K, Vogel SS, et al. Defective membrane repair in dysferlin-deficient muscular dystrophy. *Nature.* 2003;423(6936):168-172.
8. Farini A, Sitzia C, Erratico S, Meregalli M, Torrente Y. Influence of immune responses in gene/stem cell therapies for muscular dystrophies. *BioMed research international.* 2014;2014:818107.
9. Han R, Rader EP, Levy JR, Bansal D, Campbell KP. Dystrophin deficiency exacerbates skeletal muscle pathology in dysferlin-null mice. *Skeletal muscle.* 2011;1(1):35.
10. de Morree A, Flix B, Bagaric I, et al. Dysferlin regulates cell adhesion in human monocytes. *The Journal of biological chemistry.* 2013;288(20):14147-14157.
11. Choi JH, Park YE, Kim SI, et al. Differential immunohistological features of inflammatory myopathies and dysferlinopathy. *Journal of Korean medical science.* 2009;24(6):1015-1023.
12. Gallardo E, Rojas-Garcia R, de Luna N, Pou A, Brown RH, Jr., Illa I. Inflammation in dysferlin myopathy: immunohistochemical characterization of 13 patients. *Neurology.* 2001;57(11):2136-2138.
13. Fanin M, Angelini C. Muscle pathology in dysferlin deficiency. *Neuropathology and applied neurobiology.* 2002;28(6):461-470.

14. Cohen TV, Cohen JE, Partridge TA. Myogenesis in dysferlin-deficient myoblasts is inhibited by an intrinsic inflammatory response. *Neuromuscular disorders : NMD.* 2012;22(7):648-658.

15. Nemoto H, Konno S, Sugimoto H, et al. Anti-TNF therapy using etanercept suppresses degenerative and inflammatory changes in skeletal muscle of older SJL/J mice. *Experimental and molecular pathology.* 2011;90(3):264-270.

16. Halevy O, Genin O, Barzilai-Tutsch H, et al. Inhibition of muscle fibrosis and improvement of muscle histopathology in dysferlin knock-out mice treated with halofuginone. *Histology and histopathology.* 2013;28(2):211-226.

17. Walter MC, Reilich P, Thiele S, et al. Treatment of dysferlinopathy with deflazacort: a double-blind, placebo-controlled clinical trial. *Orphanet journal of rare diseases.* 2013;8:26.

18. Narayanaswami P, Weiss M, Selcen D, et al. Evidence-based guideline summary: Diagnosis and treatment of limb-girdle and distal dystrophies: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. *Neurology.* 2014;83(16):1453-1463.

19. Rocha CT, Hoffman EP. Limb-girdle and congenital muscular dystrophies: current diagnostics, management, and emerging technologies. *Current neurology and neuroscience reports.* 2010;10(4):267-276.

20. de Greef JC, Lemmers RJ, Camano P, et al. Clinical features of facioscapulohumeral muscular dystrophy 2. *Neurology.* 2010;75(17):1548-1554.

21. Tawil R, Shaw DW, van der Maarel SM, Tapscott SJ. Clinical trial preparedness in facioscapulohumeral dystrophy: Outcome measures and patient access: 8-9 April 2013, Leiden, The Netherlands. *Neuromuscular disorders : NMD.* 2014;24(1):79-85.

22. Frisullo G, Frusciante R, Nociti V, et al. CD8(+) T cells in facioscapulohumeral muscular dystrophy patients with inflammatory features at muscle MRI. *Journal of clinical immunology.* 2011;31(2):155-166.

23. Arahata K, Ishihara T, Fukunaga H, et al. Inflammatory response in facioscapulohumeral muscular dystrophy (FSHD): immunocytochemical and genetic analyses. *Muscle & nerve. Supplement.* 1995(2):S56-66.

24. Deenen JC, Arnts H, van der Maarel SM, et al. Population-based incidence and prevalence of facioscapulohumeral dystrophy. *Neurology.* 2014;83(12):1056-1059.

25. Brouwer OF, Padberg GW, Wijmenga C, Frants RR. Facioscapulohumeral muscular dystrophy in early childhood. *Archives of neurology.* 1994;51(4):387-394.

26. Chen TH, Lai YH, Lee PL, et al. Infantile facioscapulohumeral muscular dystrophy revisited: Expansion of clinical phenotypes in patients with a very short EcoRI fragment. *Neuromuscular disorders : NMD.* 2013;23(4):298-305.

27. Padberg GW, Brouwer OF, de Keizer RJ, et al. On the significance of retinal vascular disease and hearing loss in facioscapulohumeral muscular dystrophy. *Muscle & nerve. Supplement.* 1995(2):S73-80.

28. Statland JM, Sacconi S, Farmakidis C, Donlin-Smith CM, Chung M, Tawil R. Coats syndrome in facioscapulohumeral dystrophy type 1: frequency and D4Z4 contraction size. *Neurology.* 2013;80(13):1247-1250.

29. van der Maarel SM, Miller DG, Tawil R, Filippova GN, Tapscott SJ. Facioscapulohumeral muscular dystrophy: consequences of chromatin relaxation. *Current opinion in neurology.* 2012;25(5):614-620.

30. Lemmers RJ, Tawil R, Petek LM, et al. Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2. *Nature genetics.* 2012;44(12):1370-1374.

31. Klinge L, Eagle M, Haggerty ID, Roberts CE, Straub V, Bushby KM. Severe phenotype in infantile facioscapulohumeral muscular dystrophy. *Neuromuscular disorders : NMD.* 2006;16(9-10):553-558.

32. Lutz KL, Holte L, Kliethermes SA, Stephan C, Mathews KD. Clinical and genetic features of hearing loss in facioscapulohumeral muscular dystrophy. *Neurology.* 2013;81(16):1374-1377.

33. Lemmers RJ, Goeman JJ, Van Der Vliet PJ, et al. Inter-individual differences in CpG methylation at D4Z4 correlate with clinical variability in FSHD1 and FSHD2. *Human molecular genetics.* 2014.

34. Snider L, Geng LN, Lemmers RJ, et al. Facioscapulohumeral dystrophy: incomplete suppression of a retrotransposed gene. *PLoS genetics.* 2010;6(10):e1001181.

35. Geng LN, Yao Z, Snider L, et al. DUX4 activates germline genes, retroelements, and immune mediators: implications for facioscapulohumeral dystrophy. *Developmental cell.* 2012;22(1):38-51.

36. Tasca G, Pescatori M, Monforte M, et al. Different molecular signatures in magnetic resonance imaging-staged facioscapulohumeral muscular dystrophy muscles. *PloS one.* 2012;7(6):e38779.

37. Hollingsworth KG, de Sousa PL, Straub V, Carlier PG. Towards harmonization of protocols for MRI outcome measures in skeletal muscle studies: consensus recommendations from two TREAT-NMD NMR workshops, 2 May 2010, Stockholm, Sweden, 1-2 October 2009, Paris, France. *Neuromuscular disorders : NMD.* 2012;22 Suppl 2:S54-67.

38. Friedman SD, Poliachik SL, Carter GT, Budech CB, Bird TD, Shaw DW. The magnetic resonance imaging spectrum of facioscapulohumeral muscular dystrophy. *Muscle & nerve.* 2012;45(4):500-506.

39. Kan HE, Klomp DW, Wohlgemuth M, et al. Only fat infiltrated muscles in resting lower leg of FSHD patients show disturbed energy metabolism. *NMR in biomedicine.* 2010;23(6):563-568.

40. Azzabou N, Loureiro de Sousa P, Caldas E, Carlier PG. Validation of a generic approach to muscle water T2 determination at 3T in fat-infiltrated skeletal muscle. *Journal of magnetic resonance imaging : JMRI.* 2014.

41. Janssen BH, Voet NB, Nabuurs CI, et al. Distinct disease phases in muscles of facioscapulohumeral dystrophy patients identified by MR detected fat infiltration. *PloS one.* 2014;9(1):e85416.

42. Statland JM, McDermott MP, Heatwole C, et al. Reevaluating measures of disease progression in facioscapulohumeral muscular dystrophy. *Neuromuscular disorders : NMD.* 2013;23(4):306-312.

43. Lek A, Rahimov F, Jones PL, Kunkel LM. Emerging preclinical animal models for FSHD. *Trends in molecular medicine.* 2015.

44. Tawil R, McDermott MP, Pandya S, et al. A pilot trial of prednisone in facioscapulohumeral muscular dystrophy. FSH-DY Group. *Neurology.* 1997;48(1):46-49.

45. Kissel JT, McDermott MP, Mendell JR, et al. Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumeral dystrophy. *Neurology.* 2001;57(8):1434-1440.

46. Tawil R. Facioscapulohumeral muscular dystrophy. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics.* 2008;5(4):601-606.

47. Mathews MB, Bernstein RM. Myositis autoantibody inhibits histidyl-tRNA synthetase: a model for autoimmunity. *Nature.* 1983;304(5922):177-179.

48. Chatterjee S, Prayson R, Farver C. Antisynthetase syndrome: not just an inflammatory myopathy. *Cleveland Clinic journal of medicine.* 2013;80(10):655-666.

49. Chinoy H, Adimulam S, Marriage F, et al. Interaction of HLA-DRB1*03 and smoking for the development of anti-Jo-1 antibodies in adult idiopathic inflammatory myopathies: a European-wide case study. *Annals of the rheumatic diseases.* 2012;71(6):961-965.

50. Mahler M, Miller FW, Fritzler MJ. Idiopathic inflammatory myopathies and the anti-synthetase syndrome: A comprehensive review. *Autoimmunity reviews.* 2014.

51. Janssen BH, Pillen S, Voet NB, Heerschap A, van Engelen BG, van Alfen N. Quantitative muscle ultrasound versus quantitative MRI in facioscapulohumeral dystrophy. *Muscle & nerve.* 2014.

52. Kan HE, Scheenen TW, Wohlgemuth M, et al. Quantitative MR imaging of individual muscle involvement in facioscapulohumeral muscular dystrophy. *Neuromuscular disorders : NMD.* 2009;19(5):357-362.

53. Wattjes MP, Kley RA, Fischer D. Neuromuscular imaging in inherited muscle diseases. *European radiology.* 2010;20(10):2447-2460.

54. Personius KE, Pandya S, King WM, Tawil R, McDermott MP. Facioscapulohumeral dystrophy natural history study: standardization of testing procedures and reliability of measurements. The FSH DY Group. *Physical therapy.* 1994;74(3):253-263.

55. Lue YJ, Lin RF, Chen SS, Lu YM. Measurement of the functional status of patients with different types of muscular dystrophy. *The Kaohsiung journal of medical sciences.* 2009;25(6):325-333.

56. Vincent KA, Carr AJ, Walburn J, Scott DL, Rose MR. Construction and validation of a quality of life questionnaire for neuromuscular disease (INQoL). *Neurology.* 2007;68(13):1051-1057.

57. Johnson NE, Quinn C, Eastwood E, Tawil R, Heatwole CR. Patient-identified disease burden in facioscapulohumeral muscular dystrophy. *Muscle & nerve.* 2012;46(6):951-953.