2. STUDY SYNOPSIS

Name of Company:	**Name of Finished Product:**	**Name of Active Ingredient:**
aTyr Pharma, Inc.	ATYR1940	ATYR1940

Title of Study:

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

Investigators and/or Study Centers:

This study was conducted at 6 study centers in the United States (US) and European Union (EU).

Publication (reference):

None to date.

Studied Period:	**Phase of development:**
13 July, 2016, to 18 April, 2017 (Date of first patient visit to date of last patient visit)	Phase 1b/2

Objectives:

The objectives of this study were 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 facioscapulohumeral muscular dystrophy (FSHD) previously enrolled in clinical study ATYR1940-C-003 (Stage 1 only) or ATYR1940-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.

Methodology:

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

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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, were considered by the Investigator to be compliant with ATYR1940 and the study procedures, and did not meet any criterion for ATYR1940 discontinuation were eligible for participation in the current study, contingent upon Investigator and patient agreement to continue ATYR1940 treatment.

Ideally, when a patient transferred 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 was 1 week; however, a maximum duration of 3 weeks was permissible. (A window >3 weeks may have been permissible on a case-by-case basis, if required due to administrative reasons, after consultation with the Medical Monitor.)

Number of Patients (Planned and Analyzed):

No formal sample size calculation was performed. It was anticipated that up to 24 patients would be enrolled in the study.

A total of 8 patients were enrolled, including 2 with FSHD, 4 with early-onset FSHD, and 2 with LGMD2B. Of the 8 patients enrolled, 4, all with early-onset FSHD, had previously participated in Parent Study ATYR1940-C-003, and 4, 2 each with FSHD and LGMD2B, had previously participated in Parent Study ATYR1940-C-004.

Diagnosis and Main Criteria for Inclusion:

Patients who participated in either parent study ATYR1940-C-003 or ATYR1940-C-004 and completed the treatment period in the parent study; in the Investigator's opinion, demonstrated acceptable tolerability of study drug; were considered by the Investigator to be compliant with study drug and the study procedures; and did not meet any criterion for study drug discontinuation were eligible for participation in the current study, contingent upon Investigator and patient agreement to continue study drug treatment.

Test Product, Dose and Mode of Administration, Batch Number(s):

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 does not contain any preservatives or anti-microbial or bacteriostatic agents and is suitable for single-dose use by IV administration.

For the first 12 weeks in this extension study, patients received ATYR1940 at the highest tolerated dose received in the parent study; no dose adjustments were allowed during this 12-week period. After

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12 weeks, if the patient demonstrated good tolerability, the ATYR1940 dose may have been 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 were not permissible.

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

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

The lot numbers of ATYR1940 used in this study were 0000345395 and 0000368642.

Reference Therapy, Dose and Mode of Administration, Batch Number(s):

None.

Duration of Treatment:

Patients may have been treated with ATYR1940 under this protocol until ATYR1940 was approved or its development was discontinued, the study was closed by the Sponsor, or a criterion for study drug discontinuation was met.

Criteria for Evaluation:

Pharmacodynamics and Muscle Effects:

Muscle strength was assessed by manual muscle testing (MMT), and upper and lower extremity muscle function was assessed using the Brooke and Vignos scales.

The PD effects of ATYR1940 were evaluated by determination of muscle disease burden on lower extremity skeletal muscle MRI and FSHD-related inflammatory immune state in peripheral blood (including circulating immune proteins such as cytokines; ex vivo inflammatory immune protein release from peripheral blood mononuclear cells [PBMCs], and immunophenotyping [general and disease-specific] of circulating PBMCs).

Quality of Life:

Quality of life was assessed, based on the Individualized Neuromuscular Quality of Life (INQoL) questionnaire and, for patients with FSHD, the FSHD-specific Health Index (FSHD-HI) questionnaire.

Systemic Exposure:

Systemic exposure was determined through pharmacokinetic (PK) sampling.

Safety:

Safety evaluations included in physical examinations, including neurological examinations, safety laboratory tests, vital signs, pulmonary function test, pulse oximetry, and documentation of adverse

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events (AEs), including serious adverse events (SAEs). Furthermore, blood samples were collected for anti-drug antibody (ADA) titers and Jo-1 antibody levels.

Statistical Methods:

Statistical analyses of safety, PK, and PD data were primarily descriptive in nature. Continuous variables were summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables were summarized showing the number and percentage (n, %) of patients within each classification.

Summary and Conclusions:

Patient Characteristics at Study Entry:

A total of 8 patients were enrolled, including 2 with FSHD, 4 with early-onset FSHD, and 2 with LGMD2B. All 8 patients were white and 7 (88%) were male. The mean age of patients was 30 years, with a wide range of 16 to 62 years. Consistent with the entry criteria for Parent Study ATYR1940-C-003, patients from this study with early-onset FSHD were younger (range 16 to 20 years; mean 19 years) than among those from ATYR1940-C-004 with FSHD (range 33 to 44 years; mean 39 years) and LGMD2B (range 27 to 62 years; mean 45 years). Mean height, weight, and body mass index at baseline were 179.3 cm, 82.1 kg, and 25.5 kg/m^2, respectively.

For the 2 patients with LGMD2B, the age at first disease sign or symptom was 12 and 20 years, and the disease duration was 11.6 and 51.6 years. The disease severity score was 8 for both patients.

For the 4 patients with early-onset FSHD, the age at first disease sign or symptom ranged from 3 to 9 years, and the disease duration ranged from 12.9 to 18.5 years. All 4 patients had *FSHD1*. The *D4Z4* repeat number ranged from 2 to 5, and the *EcoR1* fragment size ranged from 14.0 to 23.5 kb. No patient was known to have an *SCHMD1* mutation. The disease severity score ranged from 3 to 5.

For the 2 adult patients with FSHD, the age at first disease sign or symptom was 17 and 37 years, and the disease duration was 7.6 and 17.6 years. Both patients had FSHD1. The *D4Z4* repeat number was 3 and 10, and the *EcoR1* fragment size was 17.0 and 40.0 kb. Neither patient had an *SCHMD1* mutation. The disease severity score was 3.0 and 3.5.

Summary of Pharmacodynamics:

In the small patient population evaluated, no clear trends were apparent with regard to muscle improvement or deterioration or changes in disease burden over the extension period. However, when examined on an individual patient basis, some evidence of disease stabilization, as indicated by MMT testing and Brooks and Vignos scale scores, as well as stabilization in quality of life, as indicated by INQoL scores, was observed over the cumulative, long-term study period.

Summary of Pharmacokinetics:

ATYR1940 is identical in structure to the endogenous wild-type human HARS and the same assay is

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used to measure serum concentrations of both proteins. Measurable HARS concentrations were observed for 3 patients, ranging 1.7 to 44.4 ng/mL. These baseline HARS concentrations were not subtracted from post-dose serum ATYR1940 concentrations, because the endogenous HARS concentrations were minimal in comparison ATYR1940 concentrations.

Blood samples to determine ATYR1940 serum concentrations were collected approximately every 6 weeks, at 1.5 and 4 hours after the start of the 1.5 hour (90-minute) infusion of ATYR1940. Exposure to ATYR1940 was confirmed for all patients at all post-infusion time points.

A formal analysis of the relationship between drug concentrations and patient response was neither pre-specified nor conducted.

Summary of Safety:

Seven (88%) of 8 patients experienced at least 1 treatment-emergent adverse event (TEAE). No new TEAEs of concern were observed with long-term ATYR1940 treatment. The most common TEAEs reported across both studies were nausea and fall (each 4 patients) and back pain, myalgia, and pain in extremity (each 3 patients). All other TEAEs were reported for ≤2 patients. When the current study only is considered, 7 patients experienced at least 1 TEAE, with the same common TEAEs reported at the same incidence in the current study as were seen across both studies. A brief review of all events suggested that they were likely unrelated to treatment (i.e., occurred after treatment end, resolved while on treatment, did not recur with continued dosing) or were consistent with rare myopathies with an immune component.

Across the parent and current studies, all TEAEs were Grade 1 or 2 in intensity; no ≥Grade 3 TEAEs were reported.

Across the parent and current study, 5 (63%) patients experienced at least 1 TEAE that was considered by the Investigator to be study drug-related. The only study drug-related TEAEs reported for >1 patient were headache and nausea (each 2 patients).When the current study only is considered, 4 patients experienced at least 1 study drug-related TEAE, again with the only study drug-related TEAEs reported for >1 patient being headache and nausea (each 2 patients).

No patient experienced a hematologic TEAE, including neutropenia or leukopenia, or serious or significant infection during the study.

No patient died on study. Furthermore, no patient experienced an infusion-related reaction (IRR), SAE, or TEAE leading to study withdrawal.

Two patients discontinued study drug due to rising Jo-1 Ab. One of these 2 patients experienced cutaneous rash and/or burning sensation contemporaneous with ATYR1940 infusion, not considered by the Investigator to represent an IRR.

No clinically significant trends or changes from baseline were seen in clinical laboratory test results,

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vital signs, ECGs, PFTs, or oxygen saturation.		
Conclusions: Overall, based on the results of the current study, it was concluded that longer-term treatment with ATYR1940 was well tolerated at doses up to 3.0 mg/kg weekly in patients with FSHD and LGMD, with no new safety concerns identified. Assessment of long-term treatment with ATYR1940 in a larger number of patients to better assess the PD effects of ATYR1940 for the stabilization of these rare RMIC is warranted.		
Date of the Report: 05 March, 2018		