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, Biological Activity, and Systemic Exposure of ATYR1940 in Adult Patients with Facioscapulohumeral Muscular Dystrophy (FSHD)

Investigators and/or Study Centers:

This study was conducted at 3 study centers in the United States (US) and European Union (EU).

Publication (reference):

None to date.

Studied Period:	**Phase of development:**
13 August 2015 to 14 March 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 IV ATYR1940 in adult patients with FSHD previously enrolled in clinical study ATYR1940-C-002.
- Evaluate the effects of long-term ATYR1940 treatment on clinically relevant measures of muscle strength and function, including:
- Quantitative Muscle Testing (QMT); and
- Manual muscle testing (MMT), as determined by the Investigator.
- Evaluate the effects of long-term ATYR1940 treatment on patient-reported quality of life (QOL).
- Evaluate the effects of long-term ATYR1940 treatment on muscle disease burden, based on skeletal muscle MRI.
- Explore biological and pharmacodynamic (PD) changes in the inflammatory immune state in peripheral blood.
- Determine the long-term systemic exposure to ATYR1940 through pharmacokinetic (PK) sampling.

Methodology:

Study ATYR1940-C-005 was a multi-national, multi-center, open-label extension study designed to evaluate the long-term safety, effects on muscle, PD, and systemic exposure of ATYR1940 in adult patients with FSHD previously treated in the parent study, ATYR1940-C-002. This study was conducted at the same study centers at which patients were enrolled in the parent study.

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The treatment assignment in the parent study remained blinded. Thus, given that patients assigned to placebo in the parent study received ATYR1940 for the first time in the current study, all patients were intensively monitored for safety during the first 4 weeks of ATYR1940 treatment in the current study.

Number of Patients (Planned and Analyzed):

No formal sample size calculation was performed. It was anticipated that up to 16 patients who participated in Parent Study ATYR1940-C-002 would be enrolled in the study.

A total of 9 patients who previously participated in Parent Study ATYR1940-C-002 enrolled in the current study.

Diagnosis and Main Criteria for Inclusion:

Patients who participated in Cohort 2 or 3 in the parent study completed the double-blind 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 intravenous (IV) administration.

Under the original protocol, ATYR1940 was administered as a 30-minute IV infusion. Given the occurrence of infusion-related reactions (IRRs) after repeat (>4 weeks) administration of ATYR1940 3.0 mg/kg administered as a 30-minute, 50-mL IV infusion once weekly, the protocol was amended (Amendment 2; 11 January 2016), to lengthen the infusion time to 90 minutes (decreasing infusion rate; mg/minute) and increase the infusion volume to 250 mL (thereby decreasing ATYR1940, excipient and impurity concentrations). Patients received ATYR1940 via a 90-minute IV infusion unless it was determined by the Investigator in consultation with the Medical Monitor and Sponsor that a patient should have received a lower dose level from the parent study and/or the infusion volume and dosing duration (e.g., infusion over 30 minutes) should have been adjusted, as medically indicated.

Furthermore, the 3.0 mg/kg dose was prepared for infusion in 250 mL saline as long as clinically indicated. If, in the Investigator's judgement, in consultation with the Medical Monitor, a patient required a change in infusion volume and duration, the change(s) was clearly documented.

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The lot numbers of ATYR1940 used in this study were CMC13002 and 0000345395.

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 QMT and MMT, and lower extremity muscle function was assessed using the Vignos scale.

The pharmacodynamic effects of ATYR1940 were evaluated by determination of muscle disease burden on lower extremity skeletal muscle magnetic resonance imaging (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 FSHD-specific] of circulating PBMCs).

Quality of Life:

Quality of life was assessed, based on the Individualized Neuromuscular Quality of Life (INQoL) questionnaire and the FSHD-specific Health Index (FSHD-HI) questionnaire. Additional measures of quality of life (e.g., sleep status) also were to be explored.

Systemic Exposure:

Systemic exposure was determined through 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 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.

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Summary and Conclusions:

Patient Characteristics at Study Entry:

A total of 9 patients who previously participated in Parent Study ATYR1940-C-002 enrolled in the current study. All 9 patients received ATYR1940 3 mg/kg in the current study. Of these 9 patients, 3 had previously received placebo in the parent study (Patients 02-003, 02-008, and 05-003) and thus were exposed to ATYR1940 for the first time in this extension study.

Of the 9 patients enrolled, all 9 were white and 6 (67%) were male. The mean age of patients was 53 years, with a wide range of 36 to 72 years. Mean height, weight, and body mass index at baseline was 176.4 cm, 77.8 kg, and 24.5 kg/m^2, respectively. The median duration of FSHD was 28.4 years, with a wide range of 11.2 to 56.4 years. All 9 patients had a genetic diagnosis of *FSHD1*, and 8 of 9 patients had ≥4 *D4Z4* repeats. The mean clinical severity score at baseline was 3.3, with a range of 3.0 to 4.0, indicating the patient population had mild to moderate disease symptoms.

Summary of Pharmacodynamics:

PD data were limited in this extension study. Given the limited dataset, 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 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 used to measure serum concentrations of both proteins. Per protocol, endogenous HARS concentrations were measured in the serum of all patients at the 4-week follow-up visit. Only one patient had a measurable HARS concentration of 1.26 ng/mL, while all the remaining samples were below quantifiable limits (1.0 ng/mL).

Evidence of systemic exposure to ATYR1940 was seen in this study, as evidenced by measureable serum ATYR1940 concentrations. In particular, for the 3 patients who experienced an IRR, ATYR1940 serum exposure was confirmed in samples collected immediately after the event occurred.

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

Summary of Safety:

All 9 (100%) patients experienced at least 1 treatment-emergent adverse event (TEAE). All TEAEs were Grade 1 or 2 in intensity and non-serious. Most individual TEAEs occurred in 1 patient only. TEAEs occurring in >1 patient included headache (66%), myalgia (44%), back pain and influenza (each 33%) and arthralgia, diarrhea, fatigue, hepatic enzyme increased, IRR, nasopharyngitis, pain in extremity,

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upper abdominal pain, vomiting, and wound (each 22%).

Eight (89%) patients experienced at least 1 TEAE that was considered by the Investigator to be at least possibly related to ATYR1940 (i.e., study drug-related TEAE). Study drug-related TEAEs reported by >1 patient included headache and IRR (each 33%) and arthralgia, hepatic enzyme increased, and myalgia (each 2 patients; 22%).

A brief review of all events suggested that they were perhaps unrelated to treatment (occurred after treatment end, did not recur with continued dosing, resolved while on treatment) or were consistent with past medical history or FSHD.

All TEAEs were Grade 1 or 2 in intensity and non-serious.

Three patients discontinued ATYR1940 because of a TEAE, including a Grade 2 IRR and Grade 1 flushing and diaphoresis, with these events considered by the Sponsor to be representative of an IRR.

No clinically significant trends or changes from baseline were seen in clinical laboratory test results, vital signs, ECGs, pulmonary function tests, 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 a dose of 3.0 mg/kg weekly in patients with FSHD, with no new safety concerns identified. Assessment of the PD effects of ATYR1940 for the stabilization of FSHD will require a larger number of patients.

Date of the Report: 03 January, 2018