Results of a Phase 1b/2 Study of ATYR1940 in Adolescents and Young Adults With Early-onset Facioscapulohumeral Muscular Dystrophy (FSHD) (ATYR1940-C-003)

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Introduction

Early-onset Facioscapulohumeral Muscular Dystrophy (FSHD)

- FSHD is a rare genetic autosomal dominant muscular dystrophy that results in significant disability. Patients diagnosed with FSHD typically present with symptoms in late adolescence or early adulthood.[1]
- Early-onset FSHD refers to patients who present with symptoms before the age of 18 years. Within this early-onset population are individuals who had symptoms before the age of 5 years and disease progression before the age of 10 years, often defined as "infantile-onset" FSHD.[2] These patients typically have more severe, rapidly progressive, muscle involvement, as well as extramuscular conditions such as hearing loss and retinal vascular abnormalities.[3]
- Inflammatory cell infiltration of skeletal muscles in patients with FSHD is observed and may be involved in the pathophysiology of FSHD.[4,5]
- No targeted pharmacological interventions are available for FSHD.

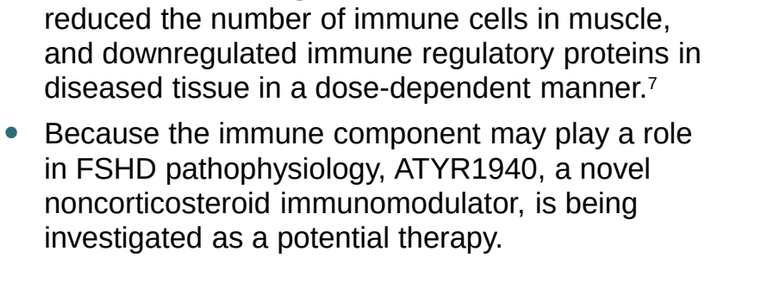
ATYR1940 for the Treatment of FSHD

- ATYR1940 (Resolaris™) is a slightly truncated form of human histidyl tRNA synthetase (HARS).
- HARS may have extracellular roles, including modulation of immune responses in skeletal muscle,[6] in addition to its established intracellular function in protein synthesis.
- In preclinical experiments using a rat model of statin-induced myopathy, ATYR1940 reduced skeletal-muscle degeneration and necrosis, reduced the number of immune cells in muscle, and downregulated immune regulatory proteins in diseased tissue in a dose-dependent manner.[7]
- Because the immune component may play a role in FSHD pathophysiology, ATYR1940, a novel noncorticosteroid immunomodulator, is being investigated as a potential therapy.

Study Design

- This was a phase 1b/2, multicenter, open-label, intrapatient, placebo run-in, dose-escalation study that evaluated the safety, tolerability, immunogenicity, and exploratory clinical assessments of intravenous (IV) ATYR1940 administered once weekly (qw).
- Study population:
  - 16–25 years old
  - Genetically established FSHD1
  - Signs or symptoms of FSHD before 10 years old
- Patients received 1 dose of placebo, then 12 doses of ATYR1940 starting at 0.3 mg/kg qw and increasing to 3 mg/kg qw (**Figure 1**).

Figure 1. Study Design



*Patients who completed this study could enter a long-term extension study.
qw = once weekly.

Key Study Endpoints

- Safety and tolerability were assessed by:
  - Incidence of adverse events (AEs), and anti-drug antibody (ADA) titer and Jo-1 (anti-HARS) antibody levels.
  - Standard clinical evaluations (ie, electrocardiograms, pulmonary function tests, laboratory investigations).
- Clinical activity was assessed by a change from baseline to Week 14 using:
  - Manual Muscle Testing (MMT), a validated assessment of muscle strength. Assessments were graded using a modified Medical Research Council scale.[7]
    - Ordinal scores were converted to numeric scores, and results across 14 muscle groups were used to calculate a total MMT score.
  - Individualized Neuromuscular Quality-of-Life (INQoL) questionnaire, a validated self-administered, muscle-disease–specific measure of quality of life.
- Other endpoints included magnetic resonance imaging (MRI) parameters, eye and hearing assessments, and analysis of circulating biomarkers.

Results

- 8 Patients ages 16 to 20 years were enrolled; all had FSHD1.
- All patients completed the study:
  - 1 Patient did not receive all doses of study drug due to an infusion-related reaction (IRR).
  - Individual demographics and baseline characteristics are shown in **Table 1**.

Table 1. Demographics and Baseline Characteristics

Characteristic	Early-onset FSHD, Mean (N = 8)
Age, years	17.9
Disease duration, years	13.1
Age of onset, years	6.1
Clinical severity score*	3.1
D4Z4 repeat	3.6

*FSHD-specific clinical severity score with a scale of 0.5 (facial weakness) to 5.0 (wheelchair bound).
FSHD, facioscapulohumeral muscular dystrophy.

Safety and Tolerability

- All 8 (100%) patients reported at least 1 treatment-emergent AE (TEAE) (**Table 2**).
  - All TEAEs were mild or moderate.
  - 1 Patient had a grade 2 (moderate) nonserious IRR that resolved the day of drug discontinuation.
  - No serious AEs were reported.
- No signals or trends were observed during the study regarding results from vital signs, electrocardiograms, or pulmonary functional tests.
- No evidence of general immunosuppression was noted on review of hematology and TEAEs (ie, no neutropenia, leukopenia, or serious infections).
- No clinically significant changes in indirect ophthalmoscopy, fundus findings, or optical coherence tomography.

Table 2. TEAEs in ≥ 2 patients

Preferred Term	Early-onset FSHD (N = 8) n (%)
Myalgia	3 (37.5%)
Paresthesia	3 (37.5%)
Headache	2 (25.0%)
Nasopharyngitis	2 (25.0%)
Nausea	2 (25.0%)

FSHD, facioscapulohumeral muscular dystrophy; TEAE, treatment-emergent adverse event.

Immunogenicity

- 4 of 8 patients receiving ATYR1940 had positive test results for ADA signals; these titer levels were low and did not result in clinical symptoms.
- No patients had Jo-1 antibody levels that were considered positive or equivocal for antisynthetase syndrome.

Clinical Activity

MMT

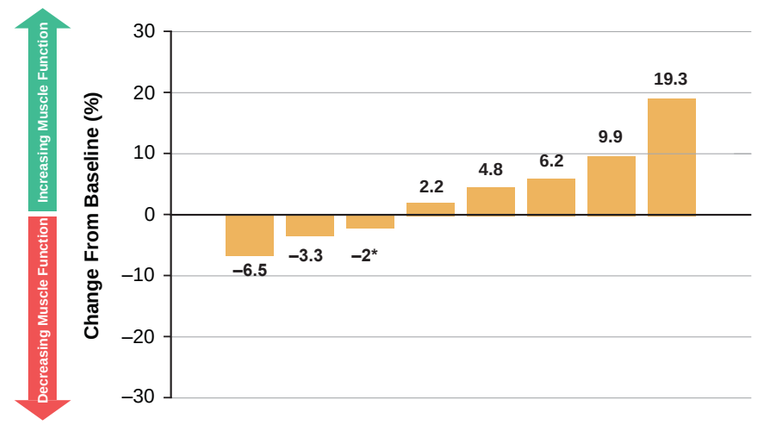
- Mean total MMT score increased by 3.8% (n = 8: range –6.5% to 19.3%).
- 5 (63%) of 8 patients had increases from baseline in total MMT scores (**Figure 2**).

INQoL

- Mean overall INQol score changed by –1.2% (n = 8: range –17.3% to 13.4%).
- 4 (67%) of 6 patients with complete data had improvements (decreases) in INQoL scores (**Figure 3**).

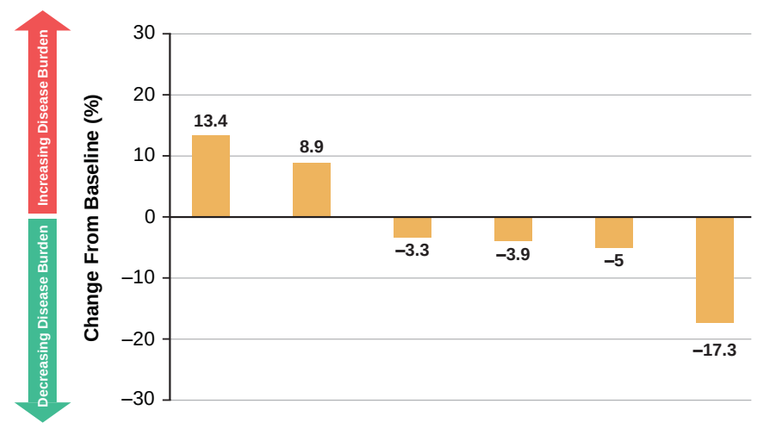
No consistent changes during the study were observed for MRI parameters or circulating biomarkers.

Figure 2. Percentage Change From Baseline to Week 14 in MMT Total Scores for Individual Patients



*Patient received only 4 doses of ATYR1940, discontinued due to insulin-related reaction.
MMT, Manual Muscle Testing.

Figure 3. Change From Baseline to Week 14 in Overall QoL Score for Individual Patients



n = 6: Only 6 of 8 patients had INQoL results at both baseline and Week 14.
INQoL; Individualized Neuromuscular Quality of Life; QoL, quality of life.

Conclusions

- In this exploratory, open-label study, ATYR1940 (Resolaris™) was generally well tolerated at doses up to 3.0 mg/kg once weekly in patients ages 16 to 20 years with early-onset FSHD.
- No signs of general immunosuppression were observed, and low-level ADA signals did not result in clinical symptoms.
- Although this study was not designed or powered to assess clinical activity, a mean increase of 3.8% in MMT scores was observed after 12 weeks of treatment.
- Mean overall INQoL score did not markedly change.
- These results support further investigation of ATYR1940 for early-onset FSHD.

References

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