A Randomized, Double-blinded, Placebo-controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Biological Activity of ATYR1940 (Resolaris™) in Adult Patients With Facioscapulohumeral Muscular Dystrophy

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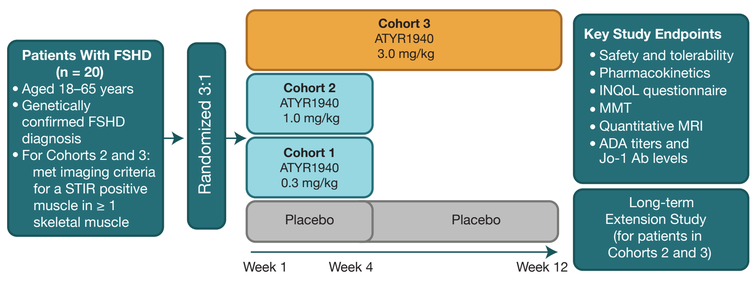
Introduction

- Facioscapulohumeral muscular dystrophy (FSHD) is a rare genetic myopathy in which immune cells invade diseased skeletal muscle and for which there are no approved treatments. The primary clinical phenotype of FSHD is debilitating skeletal muscle deterioration and weakness:
  - Estimates of FSHD prevalence vary between 1:14,000 and 1:20,000.[1]
- ATYR1940 (Resolaris™) is a slightly truncated form of human histidyl tRNA synthetase (HARS), which is 100% identical to the naturally occurring wild type molecule over the common protein sequence:
  - Aside from its established intracellular role in protein synthesis, we believe HARS also plays extracellular roles, including modulating immune responses in skeletal muscle.
  - Because the immune component may play a central role in FSHD pathophysiology,[2] immunomodulators, including ATYR1940, are being investigated as potential therapies for this disease.
- In preclinical experiments using a rat model of statin-induced myopathy, ATYR1940 reduced skeletal muscle degeneration and necrosis, reduced the numbers of immune cells in muscle, and downregulated immune regulatory proteins in diseased tissue in a dose-dependent manner.
- This first-in-patient study evaluated the safety, tolerability, pharmacokinetic (PK) properties, immunogenicity, and biological activity of ATYR1940 in adult patients with FSHD (ClinicalTrials.gov: NCT02239224).

Methods

- This Phase 1b/2, double-blinded, placebo-controlled, multiple ascending dose study randomly assigned eligible patients 3:1 to receive weekly I.V. ATYR1940 (Cohort 1: 0.3 mg/kg; Cohort 2: 1 mg/kg; Cohort 3: 3 mg/kg) or placebo (**Figure 1**).

Figure 1. Study Design



Ab, antibody; ADA, antidrug antibody; FSHD, facioscapulohumeral muscular dystrophy; INQoL, Individualized Neuromuscular Quality of Life; MMT, manual muscle testing; MRI, magnetic resonance imaging; STIR, short tau inversion recovery.

- Key study endpoints were the evaluation of safety and tolerability as assessed by incidence of adverse events (AEs), antidrug antibody (ADA) titers, Jo-1 antibody (Ab) levels, ATYR1940 PK properties, and measures of clinical activity:
  - **Manual Muscle Testing (MMT):**
    - Motor function was assessed in 14 muscle groups and graded based on a 5-point scale.
    - For patients in Cohorts 1 and 2, MMT was assessed during screening; at Week 3; Week 4, Day 4; and Week 6; for patients in Cohort 3, MMT was assessed during screening; at Week 6; Week 10; and Week 14.
  - **Individualized Neuromuscular Quality of Life (INQoL) Questionnaire:**
    - A validated muscle disease-specific quality of life measure, with 45 questions within 10 sections. The questionnaire focuses on 4 dimensions: Symptoms, Life Domains, Treatment Effects, and Overall Quality of Life. Overall INQoL score is derived from Life Domains and comprises 5 subsections: Activities, Independence, Social Relationships, Emotions, and Body Image.
    - The self-administered questionnaire was completed during screening and at Week 6 in all cohorts as well as at Week 14 for patients in Cohort 3.
  - **Muscle Surveillance and Targeted Magnetic Resonance Imaging (MRI):**
    - Lower extremity surveillance MRI was performed during screening to identify active immune responses (as evidenced by short tau inversion recovery [STIR] positive signal).
    - The presence of ≥ 1 STIR-positive muscle as assessed by a central reviewer was an inclusion criterion for this study (Cohorts 2 and 3).
    - STIR-positive muscles were monitored using targeted quantitative MRI for the analysis of fatty infiltration, inflammation, and muscle volume.

Results

- All patients completed the study; however, 1 patient did not receive all doses of study drug due to an AE of infusion-relation reaction (IRR).
- All patients had FSHD Type 1; patient demographics and characteristics are shown in **Table 1.**

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Placebo (n = 5)	COHORT 1 ATYR1940 0.3 mg/kg (n = 3)	COHORT 2 ATYR1940 1.0 mg/kg (n = 6)	COHORT 3 ATYR1940 3.0 mg/kg (n = 6)
Median age, years (range)	52.0 (39–66)	53.0 (25–55)	46.0 (33–52)	39.5 (25–72)
Male, %	80.0	66.7	33.3	66.7
White, %	100	100	100	100
Mean BMI, kg/m^2 (SD)	28.9 (3.2)	28.6 (1.8)	25.3 (4.6)	22.5 (5.0)
Median disease duration, years (range)	18.6 (4.4–24.8)	6.2 (2.8–21.8)	22.6 (10.2–41.1)	23.0 (9.3–56.4)
Mean FSHD clinical severity score (SD)	2.7 (0.7)	2.5 (0.9)	3.7 (0.5)	3.0 (0.8)

BMI, body mass index; FSHD, facioscapulohumeral muscular dystrophy; SD, standard deviation.

Safety and Tolerability Profile

- ATYR1940 was generally well tolerated across all dose groups (**Table 2**).
- All treatment-emergent AEs (TEAEs) were Grades 1 or 2 (mild or moderate in intensity):
  - No dose-response relationship was suggested in the intensity and incidence of events.
- One patient experienced 3 successive IRR events; this was assessed as an AE by the investigator, but was considered a medically important event by the sponsor and was upgraded to a serious AE.
- No trends in hematology or serum chemistries were observed.
- No signals or trends in electrocardiograms or pulmonary function tests were observed.
- TEAEs reported for ≥ 2 patients treated with ATYR1940 are shown in **Table 2.**

Table 2. Summary of Safety

Parameter, n* (%)	Placebo (n = 5)	COHORT 1 ATYR1940 0.3 mg/kg (n = 3)	COHORT 2 ATYR1940 1.0 mg/kg (n = 6)	COHORT 3 ATYR1940 3.0 mg/kg (n = 6)
TEAEs	5 (100)	3 (100)	6 (100)	6 (100)
Treatment-related	0	0	0	0
Grade ≥ 3 TEAEs	0	0	0	0
Treatment-related	0	0	0	0
SAEs	0	0	0	1†
Deaths	0	0	0	0
Most common TEAEs				
Cough	0	1 (33.3)	0	2 (33.3)
Headache	2 (40.0)	0	1 (16.7)	2 (33.3)
Presyncope	0	0	0	2 (33.3)
Arthralgia	0	2 (66.7)	0	1 (16.7)
Flushing	0	0	1 (16.7)	1 (16.7)
Nausea	0	0	2 (33.3)	0
Back pain	1 (20.0)	1 (33.3)	3 (50.0)	0
Myalgia	0	1 (33.3)	1 (16.7)	0

*Number of patients.
†Designated as SAE by sponsor.
SAE, serious adverse event; TEAE, treatment-emergent adverse event.

PK Properties

- PK was generally consistent throughout the study, with dose-proportional increases in exposure.
- The mean clearance was low, and mean volume of distribution at steady state was small, with a mean terminal half-life of 3–5 hours.

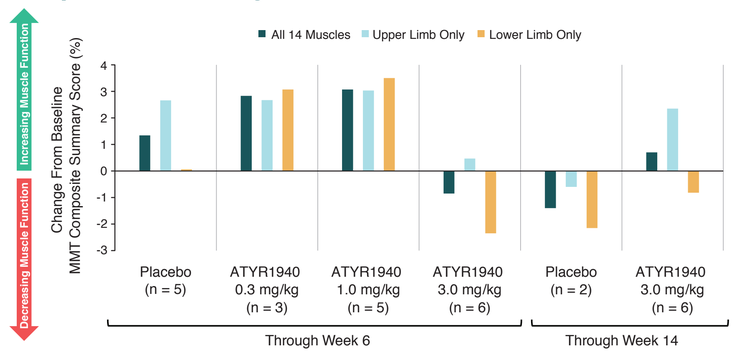
Immunogenicity Profile

- Of the 15 patients treated with ATYR1940, 6 were confirmed positive for ADA, but Ab levels fell upon cessation of therapy. No patient had titers high enough to trigger testing in a neutralizing Ab assay.
- No patients had Jo-1 Ab levels considered positive or equivocal for the assay.
- No impact of Ab levels on ATYR1940 PK was detected.

Clinical Activity

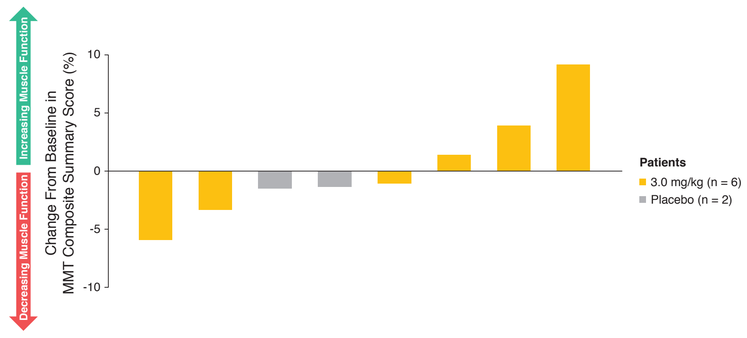
- A trend for improvement in MMT results with ATYR1940 treatment was observed compared with placebo, especially in the upper limb (**Figure 2 and 3**).

Figure 2. Percentage Change From Baseline in MMT Composite Summary Score



MMT, manual muscle testing.

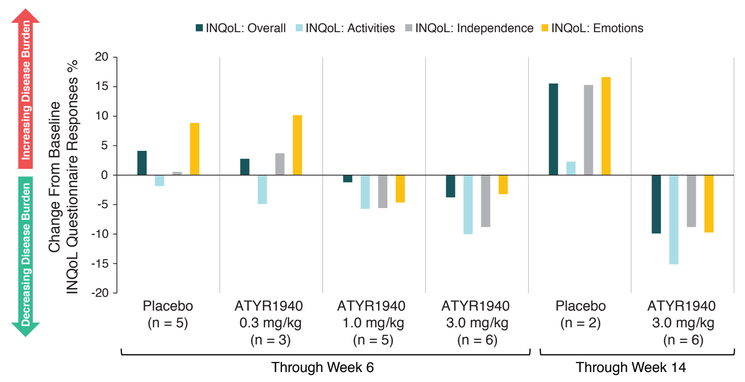
Figure 3. Percentage Change From Baseline to Week 14 in MMT Composite Summary Score for Individual Patients in Cohort 3



MMT, manual muscle testing.

- Patients treated with ATYR1940 were generally improved compared with placebo as assessed by INQoL, with patients in Cohort 3 (12 weeks) showing the greatest improvement compared with Cohort 1 and Cohort 2 (4 weeks) (**Figure 4**):
  - Patients in Cohort 3 reported ~ 10% improvement in INQoL overall responses compared with ~15% worsening in the placebo group.
  - The largest differences between Cohort 3 and placebo were seen in the Activities, Independence, and Emotions domains.
- In general, there was a good correlation between changes in INQoL and MMT, whereby all patients who experienced an improvement in muscle function also showed improvement in INQoL scores.

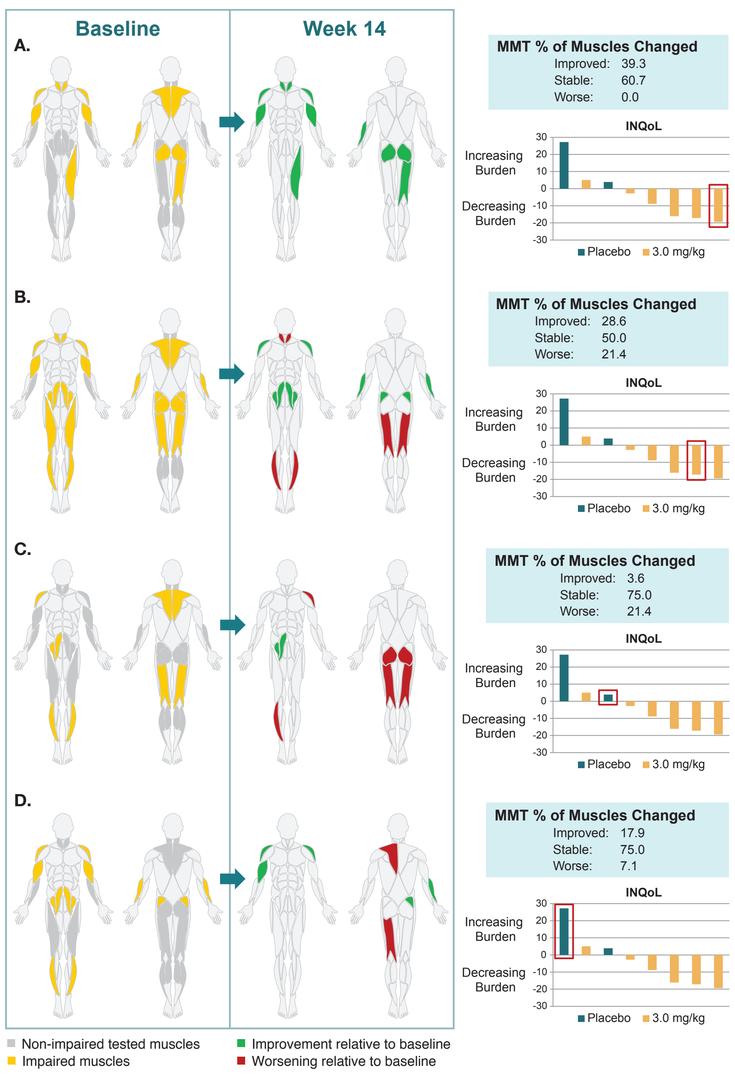
Figure 4. Percentage Change From Baseline in INQoL Questionnaire Response



INQoL, Individual Neuromuscular Quality of Life.

- In surveillance and targeted quantitative MRI scans of patients treated with placebo or ATYR1940, we observed:
  - Significant measurement variability was seen, driven in part by alignment, motion artifact, and muscle heterogeneity.
  - Little change in STIR, Dixon fat fraction percentage, or quantitative T2 (indicative of the presence of inflammation) in targeted muscles in either the ATYR1940 or placebo groups.
- No elevation from baseline in circulating human biomarker levels in plasma was observed.
- Patient profiles are shown in **Figure 5.**

Figure 5. Efficacy Results: Change From Baseline to Week 14 in Representative Patients Treated With ATYR1940 (A, B) and Placebo (C, D)



MMT, manual muscle testing; INQoL, Individual Neuromuscular Quality of Life.

Conclusions

- ATYR1940 (Resolaris™) is generally safe in adult patients with FSHD, and was well tolerated with the exception of 1 patient who experienced 3 IRR events.
- ATYR1940 PK properties were dose-proportional and consistent throughout the study, with no measureable impact from ADA.
- Clinical activity of ATYR1940 was supported by signals of improvement in INQoL questionnaire responses and MMT measures.
- Other exploratory measures, including lower extremity targeted MRI, did not demonstrate activity:
  - Variability in image acquisition may have diminished the opportunity to demonstrate a treatment effect at 3 months.
- Patients in Cohorts 2 and 3 were allowed to enroll in the ongoing, long-term extension study investigating the safety and efficacy of ATYR1940.

References

1. Tawil R et al. *Skeletal Muscle* 2014;4:12.
2. Frisullo G et al. *J Clin Immunol* 2011;31:155.

Acknowledgements

This study was funded by aTyr Pharma, Inc.
Editorial support was provided by Oxford PharmaGenesis, Inc. and was funded by aTyr Pharma, Inc

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Presented at the 21st International Congress of the World Muscle Society; 4–8 October 2016; Granada, Spain.