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Results of a Phase 1b/2 Study of ATYR1940 in Adult Patients with Limb Girdle Muscular Dystrophy Type 2B (LGMD2B) and Facioscapulohumeral Muscular Dystrophy (FSHD) (ATYR1940-C-004)

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Introduction

- Limb girdle muscular dystrophy Type 2B (LGMD2B; dysferlinopathy) and facioscapulohumeral muscular dystrophy (FSHD) are rare genetic myopathies characterized by inflammatory cell infiltration into muscle tissue,[1] debilitating skeletal muscle deterioration, and weakness.
- Dysferlinopathies including LGMD2B are recessively inherited dystrophies with 2 distinct clinical phenotypes[2]:
  - LGMD2B: Early weakness and slowly progressing atrophy of the pelvic and shoulder girdle muscles presenting in adolescents or young adults.
  - Miyoshi myopathy: Muscle weakness and atrophy in young adults, especially in the distal parts of the legs.
- FSHD is an autosomal dominant muscular dystrophy that typically affects muscles in the face and shoulder, as well as muscles of the lower extremities.[3]
- There are no targeted pharmacological interventions for the treatment of FSHD or LGMD2B.
- ATYR1940 (Resolaris™) is a Physiocrine protein that is nearly identical to human histidyl tRNA synthetase (HARS):
  - Aside from its established intracellular role in protein synthesis, HARS is believed to have extracellular roles, including modulating immune responses in skeletal muscle.[4]
  - Because the immune component may play a role in FSHD and LGMD2B pathophysiology, ATYR1940, a novel noncorticosteroid immunomodulator, is being investigated as a potential therapy for these diseases.
- In a previous first-in-patient study of ATYR1940 (0.3–3.0 mg/kg) in adults with FSHD (ClinicalTrials.gov; NCT02239224), results demonstrated that ATYR1940 was generally well-tolerated in that patient population.[5]

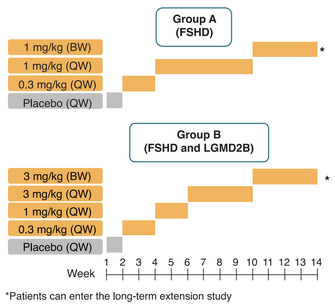
Methods

- This Phase 1b/2, multicenter, open-label, intrapatient, dose-escalation study assigned eligible patients to 1 week of placebo, then 12 weeks of ATYR1940 in 2 groups (**Figure 1**):
  - Group A: Patients with FSHD received ATYR1940 titrated up to 1.0 mg/kg twice every week.
  - Group B: Patients with LGMD2B/Miyoshi Myopathy or FSHD received ATYR1940 titrated up to 3.0 mg/kg twice every week.
  - Dose escalation was based on the patient's tolerance of the previous dose and the clinical investigator's judgment.

Figure 1. Study Design

Inclusion Criteria
- Age 18–75 years
- Established, genetically confirmed diagnosis of LGMD2B or FSHD
- Have STIR-positive muscles on MRI (FSHD/LGMD2B) or elevated muscle biomarkers (LGMD2B)

Exclusion Criteria
- Current or prior treatment with immunomodulatory agents, biologicals, or corticosteroids within 3 months
- Currently receiving curcumin or albuterol within 30 days
- Statin treatment initiation or dose adjustment within 3 months



*Patients can enter the long-term extension study

BW, twice every week; MRI, magnetic resonance imaging; QW, once weekly; STIR, short tau inversion recovery.

Key Study Endpoints

- Safety and tolerability as assessed by incidence of adverse events (AEs), antidrug antibody titers, and Jo-1 antibody levels:
  - Safety assessments also included laboratory investigations, electrocardiograms, and pulmonary function tests.
- Clinical activity, as assessed by change from baseline in:
  - *Manual Muscle Testing (MMT)*: An assessment of muscle weakness in 14 muscle groups using a modified Medical Research Council Scale.[6]
  - *Individualized Neuromuscular Quality of Life (INQoL) Questionnaire*: A validated, self-administered muscle-disease–specific measure of quality of life.
  - The primary assessment was change from baseline to week 14 of treatment.
- Other endpoints included the evaluation of changes in targeted magnetic resonance imaging (MRI) parameters and muscle biomarkers.

Results

- All patients completed the study; however, 4 patients did not receive all doses of study drug (Jo-1 levels above 1.5 U/mL, n = 2; infusion-related reaction (IRR), n = 1; withdrawal of consent, n = 1).
- Patient demographics and characteristics are shown in **Table 1**.

Table 1. Patient Baseline Disease Characteristics

Characteristic	Group A FSHD (n = 4)	Group B FSHD (n = 4)	Group B LBMD2B[a] (n = 10)
Mean disease duration, years (SD)	22.6 (13.6)	17.3 (3.5)	19.8 (15.2)
Mean age of onset, years (SD)	22.8 (12.3)	18.0 (2.7)	18.5 (4.3)
Mean clinical severity score (SD)[b]	2.63 (1.1)	2.88 (0.5)	5.7 (2.5)

[a]50% of patients had LGMD2B phenotype and 50% had Miyoshi Myopathy.
[b]For patients with FSHD: FSHD-specific Clinical Severity Score; for patients with LGMD2B: modified 10-point Gardner-Medwin and Walton scale.
SD, standard deviation.

Safety and Tolerability

- All patients experienced at least 1 treatment-emergent AE (TEAE):
  - No serious AEs (SAEs) were reported.
  - All TEAEs were Grades 1 or 2 (mild or moderate in intensity).
  - 1 Patient experienced an IRR event that was of moderate intensity and resolved the same day, following discontinuation of study drug.
  - TEAEs reported for ≥ 2 patients treated with ATYR1940 are shown in **Table 2**.
- No trends in hematology or serum chemistries were observed.
- No signals or trends in electrocardiograms or pulmonary function tests were observed.
- There was no evidence of general immunosuppression by review of hematology parameters and TEAEs (infections).

Table 2. Treatment-Emergent Adverse Events in ≥ 2 Patients

Preferred Term n (%)	Group A FSHD (n = 4)	Group B FSHD (n = 4)	Group B LBMD2B (n = 10)	Total (N = 18)
Headache	2 (50)	2 (50)	5 (50)	9 (50)
Diarrhea	2 (50)	0	2 (20)	4 (22)
Fall	0	1 (25)	3 (30)	4 (22)
Asthenia	1 (25)	0	2 (20)	3 (17)
Fatigue	2 (50)	0	1 (10)	3 (17)
Nasopharyngitis	0	1 (25)	2 (20)	3 (17)
Insomnia	0	1 (25)	1 (10)	2 (11)
Musculoskeletal pain	0	2 (50)	0	2 (11)
Nausea	0	0	2 (20)	2 (11)
Oropharyngeal pain	0	1 (25)	1 (10)	2 (11)
Pain in extremity	1 (25)	1 (25)	0	2 (11)
Presyncope	0	0	2 (20)	2 (11)
Pyrexia	0	1 (25)	1 (10)	2 (11)

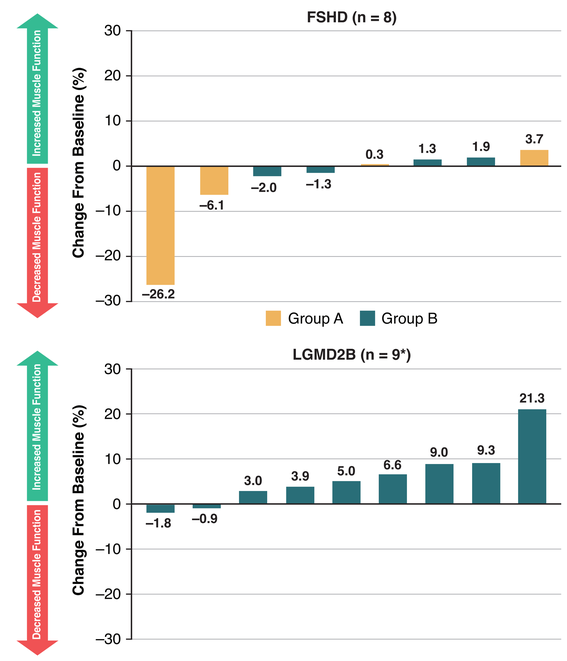
Immunogenicity

- 11 of the 18 patients treated with ATYR1940 tested positive for anti-ATYR1940 antibody signals; however, no patient had titers high enough to trigger testing in a neutralizing antibody assay.
- No patients had Jo-1 (antisynthetase) antibody levels that were considered positive or equivocal for antisynthetase syndrome:
  - 2 Patients were discontinued from treatment due to elevated Jo-1 antibody levels above the protocol-specified threshold of ≥1.5 U/mL.

Efficacy

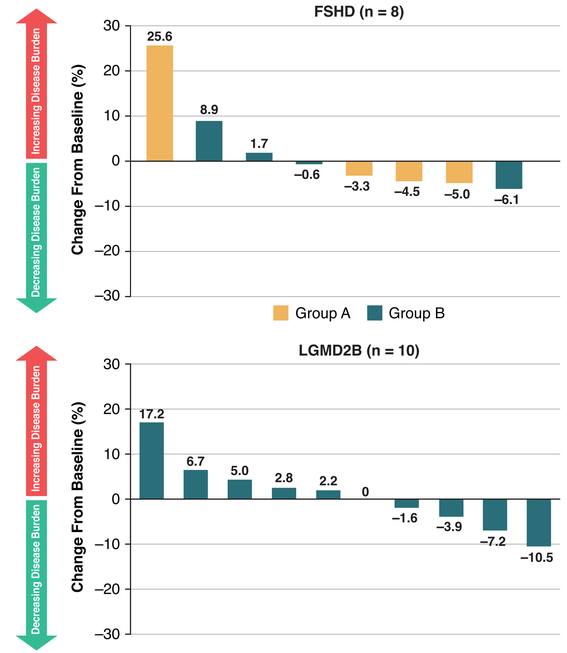
- Patients treated with ATYR1940 generally demonstrated improved muscle function as assessed by MMT (**Figure 2**):
  - In patients with FSHD (Group A and B), mean overall MMT scores did not change markedly from baseline. Equal numbers of patients (4 each) had slight improvements or declines in MMT scores over the 14-week assessment period. Of note, half of patients with FSHD (Group A) received a lower maximum dose (1 mg/kg) compared with patients in Group B (maximum dose, 3 mg/kg)
  - In patients with LGMD2B or Miyoshi Myopathy-type dysferlinopathies (Group B), 7 out of 9 patients showed improvements from baseline (mean overall MMT score increase of 6.2% [range, -1.8% to 21%]).
- No clear trend was seen in INQoL assessments among patients treated with ATYR1940 (**Figure 3**):
  - For both patients with FSHD and LGMD2B, the mean overall scores did not change substantially over the 3-month treatment period
  - There were similar proportions of patients who had small decreases and patients who had small increases in INQoL scores.
- No consistent changes over time were observed for targeted MRI or circulating biomarkers.

Figure 2. Percentage Change From Baseline in Manual Muscle Testing Composite Summary Scores (at Week 14)



*One patient was excluded because they were wheelchair-bound.

Figure 3. Percentage Change From Baseline in Overall Individualized Neuromuscular Quality of Life Questionnaire Response (at Week 14)



Conclusions

- In this exploratory open-label study, ATYR1940 at doses up to 3 mg/kg administered once or twice every week was generally safe and well-tolerated in patients with FSHD and LGMD2B:
  - Most TEAEs were mild or moderate in intensity, and no SAEs occurred.
  - Only 1 patient experienced an IRR event, which was moderate in intensity and resolved upon treatment discontinuation.
- Although this study was not designed or powered to assess efficacy, a mean increase in MMT of 6.2% was observed in patients with LGMD2B after 12 weeks of treatment.
- These results support further investigation of ATYR1940 in patients with LGMD2B or FSHD.

References

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Disclosures

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