Efficacy and Safety of Omaveloxolone for Friedreich Ataxia: Four-Months Real-Life Data

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The most common early-onset progressive hereditary **cerebellar ataxia.**

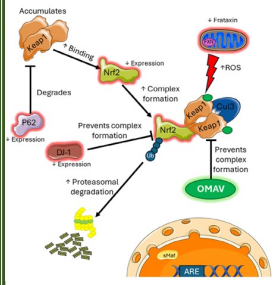
Caused by biallelic GAA trinucleotide expansions in the ***FXN* gene.**

FRDA

Frataxin: a mitochondrial protein making cells of cerebellum, dorsal root ganglia, heart and liver sensitive to **oxidative stress**

Disease manifestation:

- Cerebellar ataxia (gait and limb ataxia, dysarthria)
- Peripheral neuropathy (sensory loss, areflexia)
- Spasticity and pyramidal signs
- Optic atrophy and oculomotor disturbances
- Skeletal deformities (scoliosis, pes cavus)
- Hypertrophic cardiomyopathy and arrythmias
- Diabetes mellitus



Omaveloxolone activate Nrf2, a molecule with a pivotal role in cellular antioxidant defenses and in reducing transcription of pro-inflammatory genes, which expression is diminished in FRDA patients.

MOXIe study:

a phase-3 randomized control trial

Improved mFARS score of **-2.40** points compared to placebo after **48 weeks**.

Delayed-start analysis confirmed the persistence of benefit, with a maintained mFARS difference of **-2.91** points after **72 weeks**.

Approved by **FDA** and **EMA** in 2023 and 2024.

Key Disease Features of FRDA **Not Assessed** in the MOXIe Study:

- Cardiomyopathy
- Diabetes mellitus
- Skeletal deformities
- Optic atrophy
- Dysphagia
- Cognitive impairment

AIM: To assess clinically efficacy and safety of Omaveloxolone over **4 months** in a real-life FRDA cohort.

METHODS: Prospective, observational, real-life study on **20 consecutive FRDA patients**

- Eligibility: AIFA criteria (age ≥16 yrs, mFARS <80)
- Baseline assessments:
  - Demographics, GAA1 repeat length, disease duration
  - Neurological: mFARS, SARA, CCAS
  - Blood tests: liver enzymes, bilirubin, lipids, glucose, HbA1c, NT-proBNP, creatinine/eGFR
  - Cardiac: echocardiography, 24h Holter ECG
  - Neuropathy: modified TNS (mTNS)
- Follow-up (3–6 months):
  - mFARS, SARA, PGI-C
  - Adverse events
  - Monthly blood tests (first 3 months)

RESULTS:

- **Demographical** characteristics: 5 female, age mean **40.7**±18.2, disease durations mean **21.1**±11.9.
- **Baseline clinical** characteristics:
  - **Baseline mFARS scores** mean 51.6 ± 16.9
  - **Baseline SARA scores** mean 19.4 ± 7.7
  - CCAS scale classification: 6 Definite, 5 Possible, and 9 Absent
- The most frequently reported **clinical features** were:
  - **Ventricular cardiac hypertrophy** (13 pts/20)
  - **Pes cavus** deformity (10 pts/20)
  - **Polyneuropathy** (5 mild/13 moderate/2 severe)
  - **Diabetes mellitus** (2 pts/20)

After 4 months of treatment

- **Clinical scales**

After 4 months of omaveloxolone treatment, mean **mFARS slightly improved** (51.5±16.9, p=0.054) (Fig 1.A, 1.C), while SARA remained stable (19.3±8.3, p=0.965) (Fig 1.B).

- **Patient perception**

Mean **PGI-C** was 3.4 ± 0.7, reflecting **minimal improvement** (Fig 1.D):

- 11 no change (4)
- 6 minimal improvement (3)
- 3 much improvement (2)
- No patients reported worsening

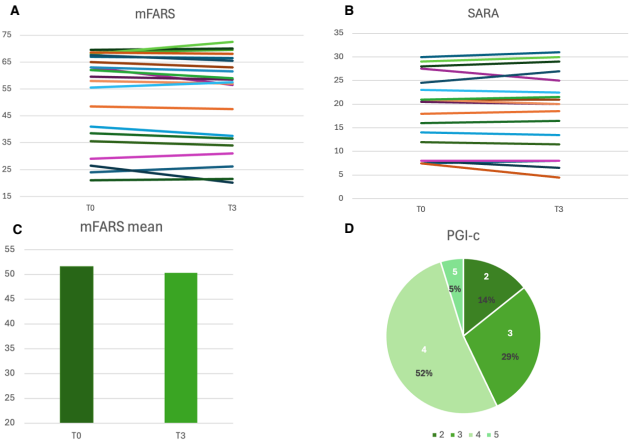


Figure 1. (**A**, **B**) Individual changes in mFARS and SARA scores over 4 months of treatment; (**C**) Mean mFARS score at baseline and after 4 months of treatment; (**D**) Distribution of PGI-c percentages among patients (Patient Global Impression of Change, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse).

ADVERSE EVENT	N of Pts (n)	Percentage (%)
Gastrointestinal symptoms:	11	55%
Gastric intolerance	5	25%
Transient diarrhea	3	15%
Constipation	1	5%
Appetite reduction	2	10%
Muscular cramps	4	20%
Headache	3	15%
Somnolence	2	10%
PATIENTS WITH AES	15	75%
TREATMENT DISCONTINUATION		
Transient	3	15%

Table 1. Summary of number and percentage of adverse events and treatment discontinuation

Laboratory findings

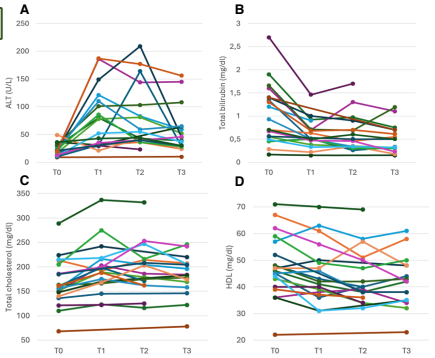


Figure 2. Laboratory findings during omaveloxolone treatment.
(**A**) Individual trajectories of ALT levels showing transient increases during treatment, elevations observed in 13/20 patients (65%). (**B**) Total bilirubin levels remained stable during treatment; 9/20 patients (45%) had elevated bilirubin already at baseline. (**C**) Changes in total cholesterol levels with a trend toward increase (baseline: 166.9±47.4 mg/dl; T3:182±42.8), requiring lipid-lowering therapy in 3 cases. (**D**) HDL cholesterol levels showed a progressive decline over time (baseline:47.7±11.4 mg/dl; T3:41.9±9.7).

Conclusions: This preliminary real-life experience suggests that omaveloxolone is generally well tolerated; no worsening in mFARS scores was observed with a slight improvement in some patients. Patient satisfaction, assessed by the PGI-c, was overall positive. A rise in ALT levels was recorded in many patients, not associated with bilirubin increase, together with a trend toward higher cholesterol and lower HDL values.

References:
1. Pandolfo M. Friedreich ataxia: the clinical picture. J Neurol. 2009;256(Suppl 1):3-8; 2. Naghipour S, Corben LA, Hulme AJ, Dottori M, Delatycki MB, Lees JG, Lim SY. Omaveloxolone for the Treatment of Friedreich Ataxia: Efficacy, Safety, and Future Perspectives. Mov Disord. 2025 Feb;40(2):226-230. doi: 10.1002/mds.30070. Epub 2024 Nov 19. PMID: 39559924.