ATAXIEN IM NEUROLOGISCHEN ALLTAG:

Diagnostische Abgrenzung und Therapieansätze am Beispiel der Friedreich-Ataxie

Zertifizierte Fortbildung

PD Dr. Jennifer Faber
Medizinische Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn

Dr. Wolfgang Nachbauer
Universitätsklinik für Neurologie an der Medizinische Universität Innsbruck

CMEducation
Ihr unabhängiges CME-Portal

Ataxie oder anderes Bewegungsstörungssyndrom?

Diagnostische Schlüssel zur Friedreich-Ataxie

PD Dr. Jennifer Faber
Klinik für Parkinson, Schlaf- und Bewegungsstörungen, Universitätsklinikum Bonn
Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Bonn
Klinik für Neuroradiologie, Universitätsklinikum Bonn

Interessenkonflikte

Jennifer Faber erhielt Honorare von Biogen, VICO therapeutics.

Forschungsförderung

Jennifer Faber ist gefördert durch das BMFTR, National Ataxia Foundation, Netzwerke NRW, Forschungskooperation im Rahmen von Konsortien mit UCB

Friedreich-Ataxie (FA)

Kerndaten

Erbgang:	Autosomal-rezessiv
Erkrankungsbeginn:	Meist vor dem 25. Lebensjahr
Prävalenz :	1 : 200.000
Gen:	FXN-Gen (Chromosom 9q21.11)
Mutation:	96% GAA Repeat Mutationen (66-1700 Wdhlg.[1]) in beiden Kopien des FXN Gens In 4% sog. *compound Heterozygotie* mit einer repeat Mutation und einer weiteren Mutation in der zweiten Genkopie[2]
Protein:	Frataxin – mitochondriales Protein

Weltweit häufigste vererbte Ataxie (1/200.000 Menschen) [3]
Europa: Häufigkeitsgefälle von Südwesten (1/20.000 im Südwesten) nach Nordosten (1/250.000) [4]
Äußerst selten in Subsahara-Afrika, China, Japan und Südostasien [4]

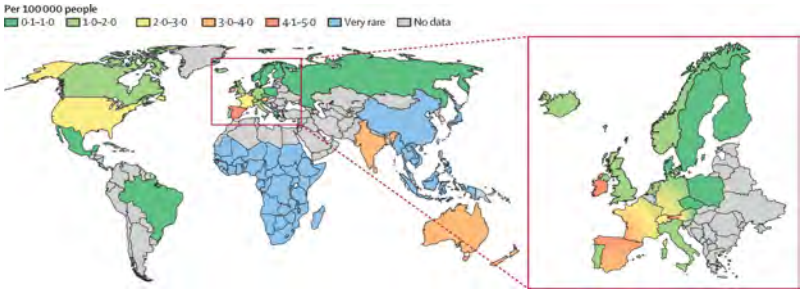


Abbildung aus: Reetz K et al., *Lancet Neurol.* 2025

1 Delatycki MB, et al.. J Med Genet 2000.
2 Galea CA, et al., Ann Neurol 2016
3 Buesch K et al., Curr Med Res Opin 2022
4 Vankan P J Neurochem 2013

Friedreich-Ataxie (FA)

Pathophysiologie

- Frataxin ist ein Mitochondriales Protein
  Beteiligt an der Bildung von Fe–S-Clustern in der Atmungskette (Komplexe I–III) und zellulären Energieproduktion (ATP).
  Rolle im Eisenzellstoffwechsel, der zellulären Redoxreaktion und der Produktion des roten Blutfarbstoffs (Häm).
- FA: Frataxin-Mangel (ca. 5-30% bei Gesunden)
- Mitochondriale Eisenakkumulation
  Beeinträchtigte NRF2-Signalübertragung und verminderte nukleäre Translokation
  Oxidativer Stress
  → Zelldysfunction
- Zelluntergang
- Organdysfunktion

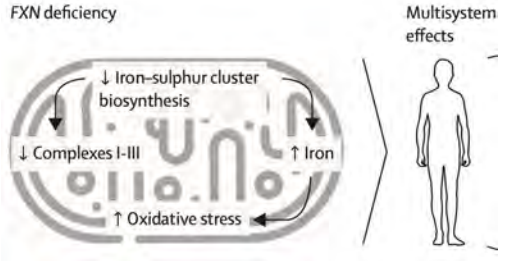


Abb. aus: Reetz, et al. Lancet Neurol 2025

Delatycki MB, et al.. J Med Genet 2000
Galea CA, et al., Ann Neurol 2016
Campuzano V, et al., Hum Mol Genet 1997
Adamec J, et al., Am J Hum Genet 2000
González-Cabo P, et al., J Neurochem 2013
Palau F., Int J Mol Med 2001

KLINISCHES BILD · Hauptsymptome

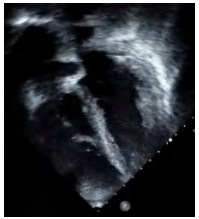
Gangataxie

Progrediente zerebelläre Ataxie; breitbasiger, ataktischer Gang; Beginn meist als Rumpfataxie (Gang, Stand)



Kardiomyopathie

Hypertrophe od. dilatative Cardiomyopathie in >90 %; Häufigste Todesursache; EKG-Veränderungen früh, Kardiologische Anbindung obligat



Skelettdeformitäten

Skoliose (>80 %), Hohlfuß (Pes cavus), Hammerzehen. Häufig erste auffällige Befunde im Kindesalter



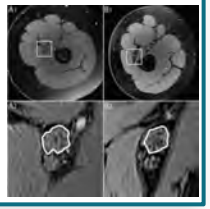
Diabetes mellitus

Regelmäßige Screenings, bereits im Kindesalter, insgs. 10–20 % der Pat., Standardtherapie



Dysarthrie, Areflexie Sensorische Störungen Spastik

Skandierende, verwaschene Sprache, Verlust von Vibrationsempfinden, Propriozeption, Fehlende Muskeleigenreflexe (ASR, PSR); Sensible Neuropathie, Spastik untere Extremitäten



Hörminderung Visusminderung Fatigue

Im Verlauf können Sehen und Hören beeinträchtigt sein; Fatigue häufiges Symptom mit hoher Alltagsrelevanz



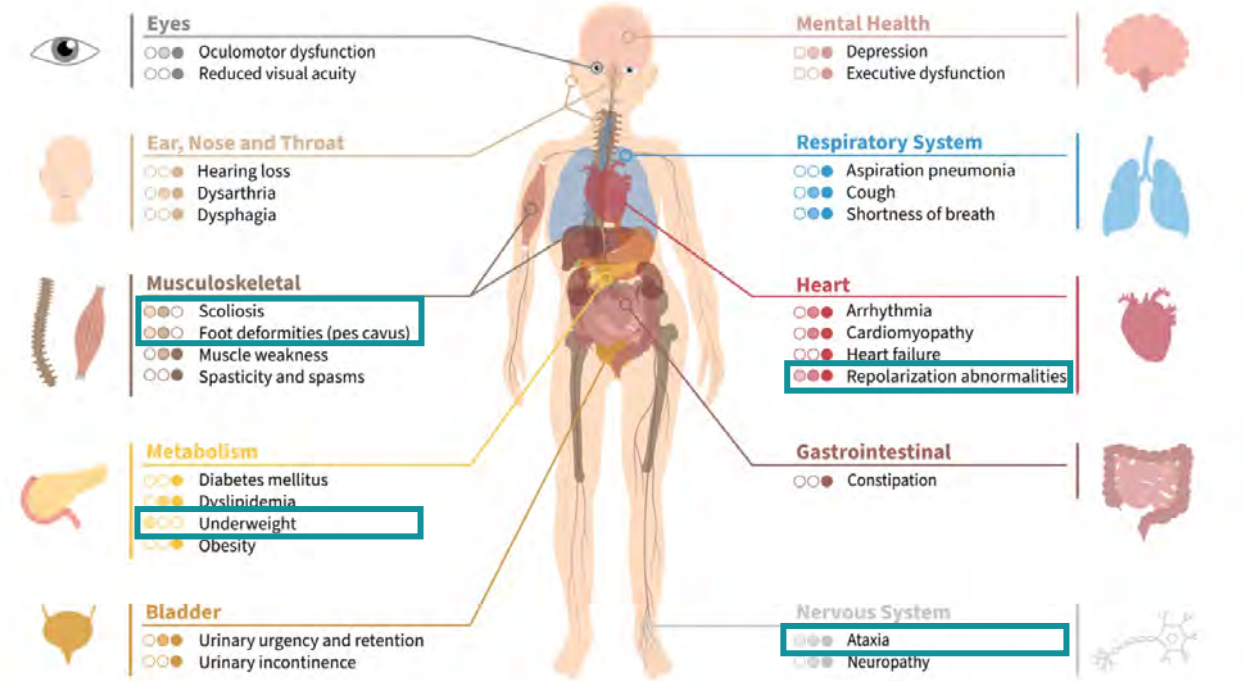




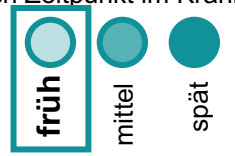
Jacobi et al., Eu J Neurol, 2025

FARA https://www.curefa.org/understanding-fa/what-is-friedreichs-ataxia

Multisystemischer Phänotyp der Friedreich Ataxie



Auftreten der Symptomatik nach Zeitpunkt im Krankheitsverlauf:



Symptomatik tritt nicht oder nur selten zum jeweiligen Zeitpunkt im Krankheitsverlauf auf:

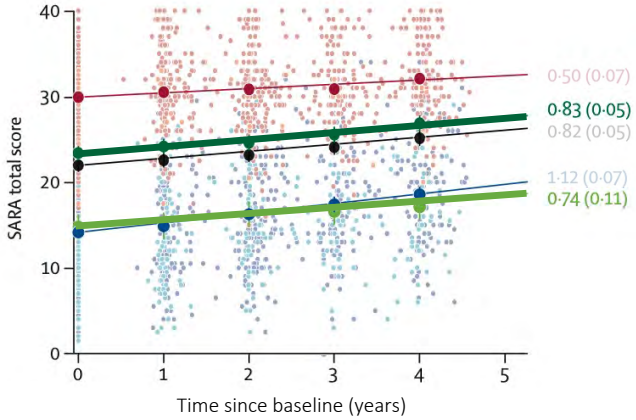
Abb. aus: Reetz, et al. Lancet Neurol 2025

Gehäuftes Vorkommen von Frataxin in Nervensystem, (Rückenmark, Kleinhirn und peripheren Nerven), Herz, Bauchspeicheldrüse, Muskulatur und braunem Fettgewebe

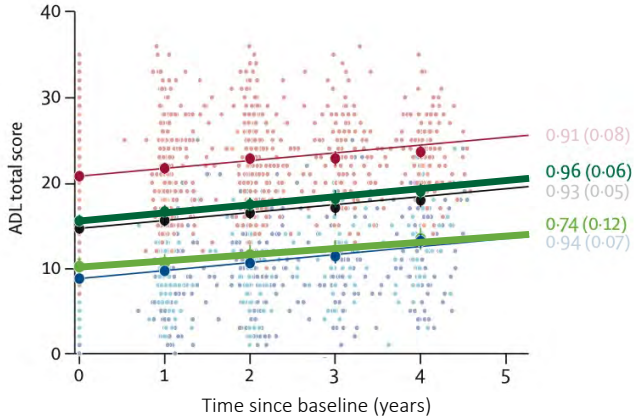
Symptombeginn Friedreich Ataxie

FA tritt am häufigsten zwischen dem 8. und 15. Lebensjahr auf.
Es wird unterschieden zwischen „typischen“ Erkrankungsbeginn, in der Regel bezogen auf ≤ 24. Lebensjahr
Und „später/ sehr später Beginn“ nach dem 25./ 40. Lebensjahr in ca. 16%.
Höhere GAA1-Repeat-Expansionen stehen in Zusammenhang mit einem früheren Symptombeginn.

Ataxieschwere



Beeinträchtigung der Alltagsaktivitäten



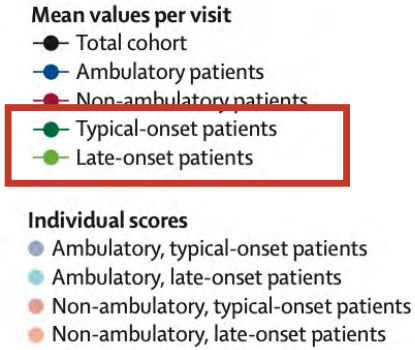


Abb. aus: Reetz, et al. Lancet Neurol 2021; EFACTS 4 year follow-up data; &
modifiziert nach: Indelicato E et al., Nat Rev Neurol. 2025, created with Biorender
Filla A et al., Am J Hum Genet 1996; Reetz, et al. Lancet Neurol., 2015

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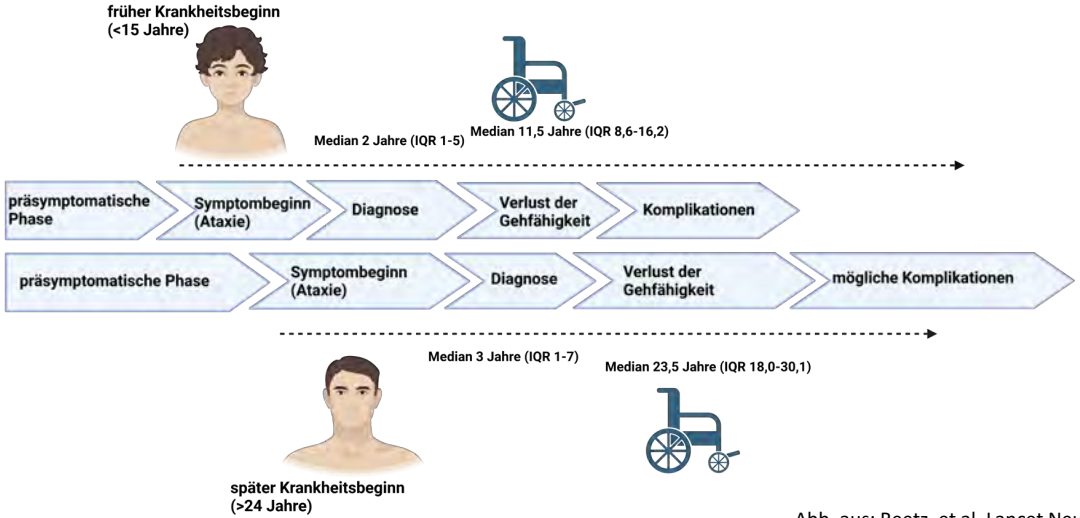

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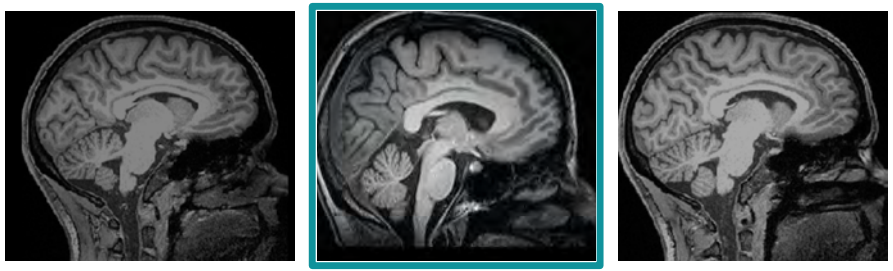
DIAGNOSTISCHE HINWEISE

Hinweisende klinische Kriterien

- Beginn vor dem 25. Lebensjahr
- **Progrediente Gangataxie**
- **cMRT ohne Hinweis auf zerebelläre Atrophie**



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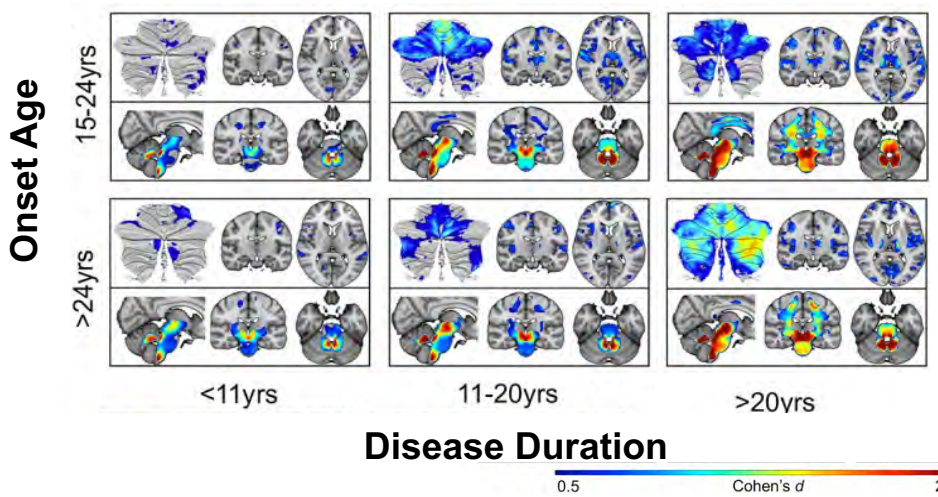

Harding, Ann Neurol, 2021

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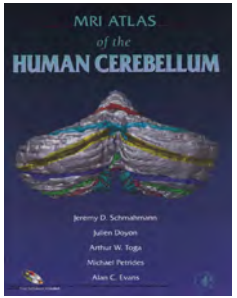

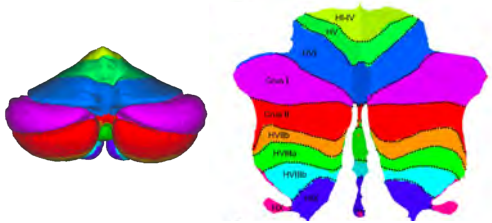

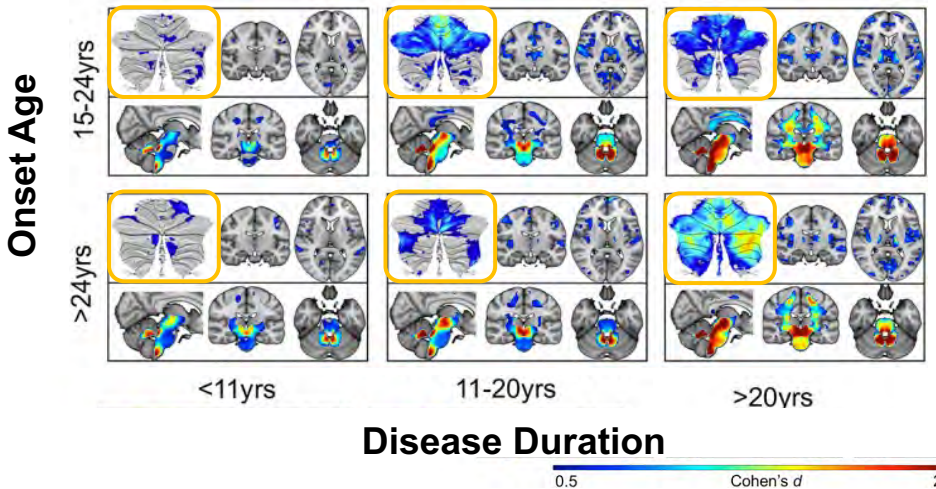

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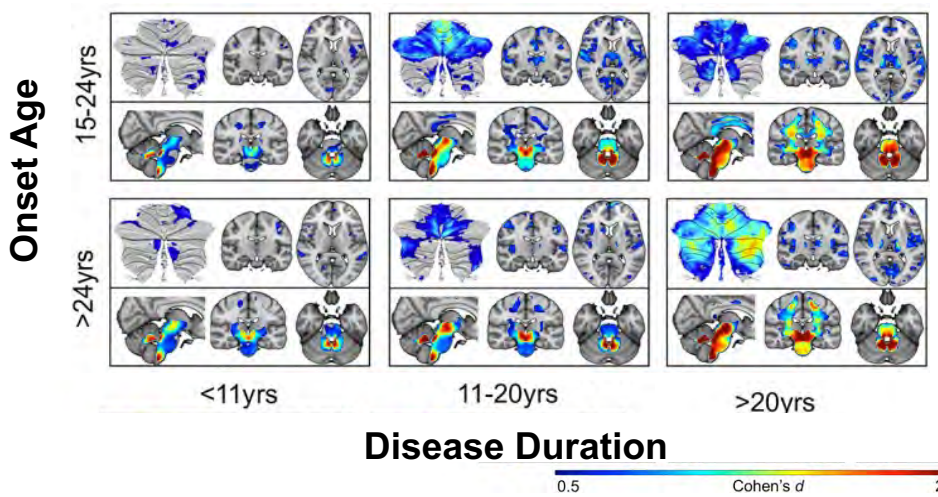

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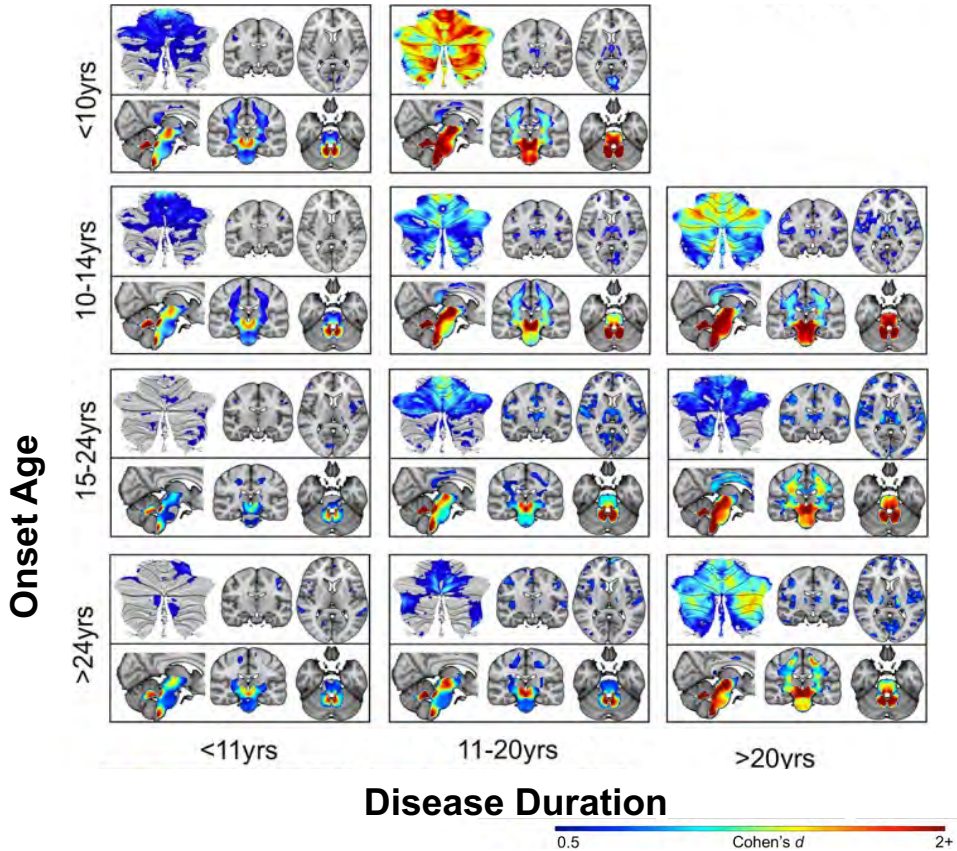
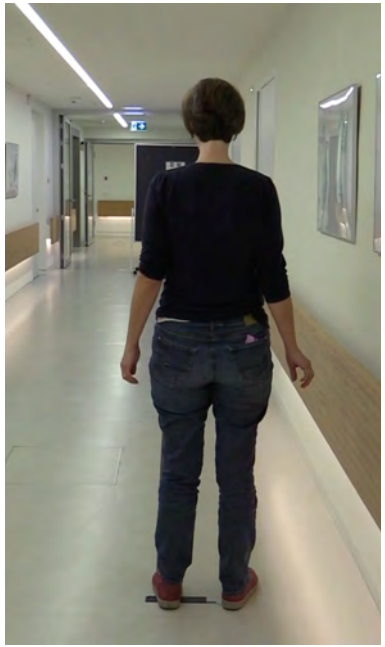


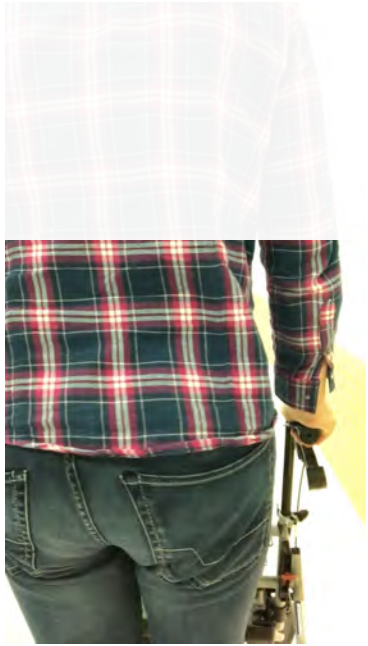
Harding, Ann Neurol, 2021

Progrediente Ataxie

Ataktisches Gangbild (SCA3)



Spastisches Gangbild (HSP)



Progrediente Ataxie

Item 1.1 - Gait

Proband is asked to walk at a safe distance parallel
to a wall including a half-turn
(turn around to face the opposite direction of gait)

Progrediente Ataxie



Progrediente Ataxie

Item 3 - Sitting

Proband is asked to sit on an examination bed
without support of feet, eyes open
and arms outstretched to the front.

Progrediente Ataxie



Progrediente Ataxie

Item 5 - Finger chase

Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s.
Proband is asked to follow the movements with his index finger, as fast and precisely as possible.
Average performance of last 3 movements is rated.

Progrediente Ataxie

Item 6 - Finger Nose Test

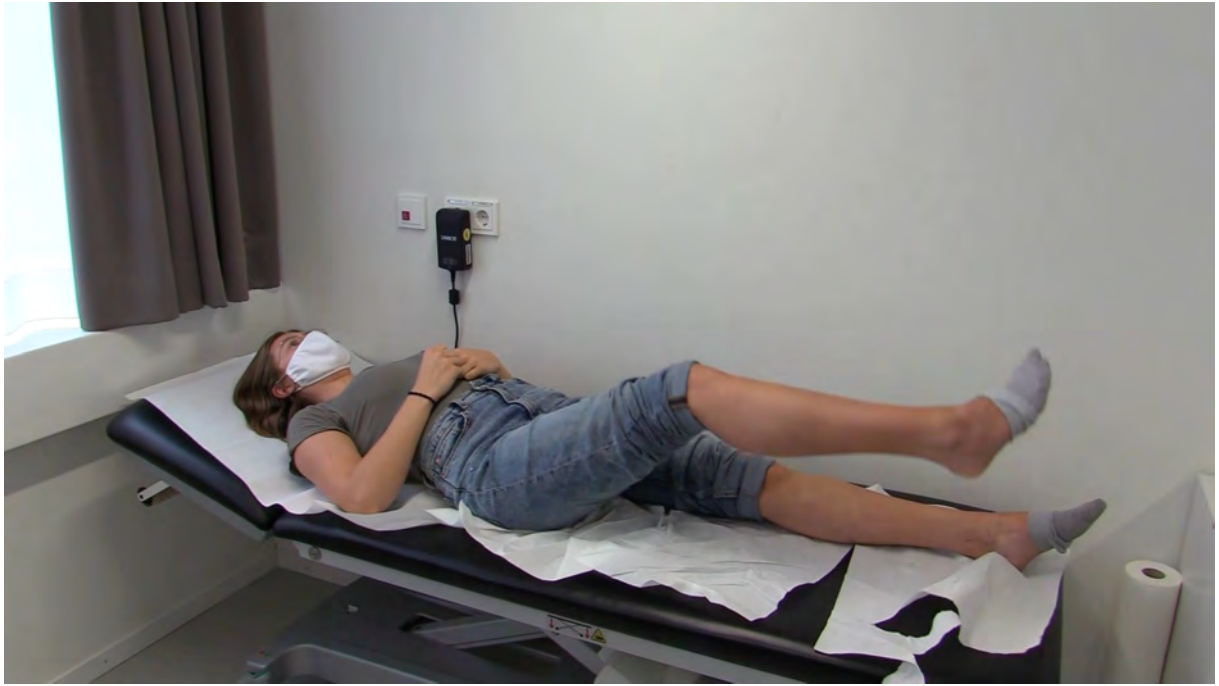
Movements are performed at moderate speed.
Average performance of movements is rated according to the amplitude of the kinetic tremor.

Progrediente Ataxie

Item 7 - Fast Alternating Hand Movements

Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

Progrediente Ataxie



Progrediente Ataxie

Item 1.2 - Gait

to walk in tandem (he
without support



Progrediente Ataxie









Progrediente Ataxie



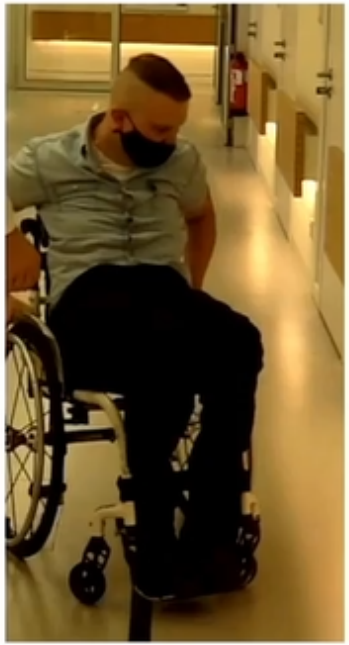








Progrediente Ataxie

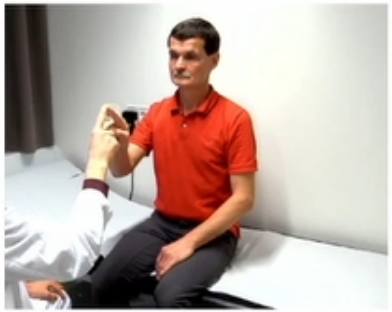


Progrediente Ataxie









Square Wave Jerks



DIAGNOSTISCHE HINWEISE

Hinweisende klinische Kriterien

- Beginn vor dem 25. Lebensjahr
- Progrediente Gangataxie
- cMRT ohne Hinweis auf zerebelläre Atrophie
- **Square Wave Jerks**
- Skoliose / Pes cavus / Hammerzehen
- Areflexie der unteren Extremitäten



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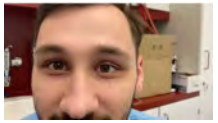

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- **Square Wave Jerks**
- **Skoliose / Pes cavus / Hammerzehen**

Häufig assoziierte Befunde

- Elektrophysiologie: Fehlen oder deutliche Reduktion sensibler Aktionspotenziale
- Kardiomyopathie (EKG: T-Wellen-Inversionen)
- Diabetes mellitus (10–20 %)
- Hörstörungen / Nystagmus / Ophthalmoplegie
- Spastik der unteren Extremitäten (Spätphase)
- Kognitive Einschränkungen (meist mild)

DIFFERENTIALDIAGNOSEN · Ataxie & Bewegungsstörungssyndrome

Hereditäre Ataxien

- Ataxie mit okulomotorischer Apraxie (AOA1/AOA2)
- SCA 1, 2, 3, 6 (Spinozerebelläre Ataxien)
- Ataxia-Teleangiectasia (Louis-Bar-Syndrom)
- ARCA2 / SYNE1-Ataxie

Metabolische Ursachen

- Vitamin-E-Mangel (AVED)
- Vitamin-B12-Mangel
- Refsum-Krankheit (Phytansäure)
- Niemann-Pick Typ C

Erworbene Ataxien

- Multiple Sklerose (zerebelläre Form)
- Paraneoplastische Kleinhirndegeneration
- Alkohol-induzierte Kleinhirnatrophie
- Medikamenten-induziert (Phenytoin, Li), selten

Andere Bewegungsstörungen

- Hereditary Spastic Paraplegia (HSP)
- Morbus Wilson (Kupferstoffwechsel)
- DRPLA (Dentatorubropallidoluysian atrophy)
- Mitochondriale Erkrankungen (MELAS, MERRF)

DIFFERENTIALDIAGNOSEN · Late onset

Hereditäre Ataxien

- RFC1 (CANVAS)
- SCA6, SCA27B (Spinozerebelläre Ataxien)

Erworbene Ataxien

- SAOA/MSA-C oligosymptomatisch
- Alkohol-induzierte Kleinhirnatrophie

Metabolische Ursachen

- Vitamin-B12-Mangel

e Ataxien

ANVAS)

CA27B (Spinozerebelläre Ataxien)

e Ataxien

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sche Ursachen



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Metabolische Ursachen

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DIAGNOSTISCHER ALGORITHMUS

1

Klinischer Verdacht

Ataxie + Areflexie + Beginn < 25 J.

2

Elektrophysiologie

Sensibel evozierte Potenziale (SEP) · Nervenleitgeschwindigkeit (NLG)

3

MRT Neuraxis

Rückenmark: Atrophie Hinterstränge · Kleinhirn: späte Atrophie

4

Kardiologische und internistische Abklärung

EKG + Echokardiographie · Kardiomyopathie-Ausschluss / -Nachweis, Screening DM

5

Genetische Testung

FXN-Gen: GAA-Repeat-Analyse · PCR + Southern Blot · >66 GAA-Repeats pathologisch, typischerweise 600-900 repeats

Von der Diagnose zur Therapie: Management und medikamentöse Therapieoptionen bei Friedreich-Ataxie

Deutscher Kongress für Parkinson und Bewegungsstörungen

17. April 2026, Leipzig

Wolfgang Nachbauer

Biogen-285457

Disclosures

Beratungs- und Sprecherhonoraria: Reata Pharmaceuticals, Biogen, Medis Therapeutics, Newbridge

Sub-investigator der MOXIe Studien (Omaveloxolon bei der Friedreich-Ataxie)

Biogen-285457

Inhalt

Nicht medikamentöse Therapie der Friedreich-Ataxie

- allgemeines Management und Empfehlungen
- Multidisziplinäres Team

Medikamentöse Therapie der Friedreich-Ataxie

- Therapieansätze und Kandidatensubstanzen
- Studiendaten Omaveloxolon
- Praktisches Vorgehen und Empfehlungen

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Einleitung

Besondere Herausforderungen im Management der FA:[1]

- Multisystem-Erkrankung
- Nicht-neurologische Beteiligung
- Unterschiedliche klinische Phänotypen (early vs. late onset)
- Erwachsene vs. Kinder

- Multidisziplinäre Therapie[2]
- Unterschiedliche Behandlungsansätze[2]
- Patienten-spezifische Therapieansätze[2]

- Limitiertes evidenzbasiertes Management[2]
- Empfehlungen basierend auf geringer Evidenz[2]

Management of the broad range of symptoms of FA

Psychiatry[3]
Ophthalmology[3]
Cardiology[3]
Endocrinology[3]
Haematology[2]
Immunology[2]
Dermatology[2]



Neurology[3]
ENT[2]
Pulmonology[4]
Gastroenterology[2]
Urology[3]
Musculoskeletal monitoring[3]

ENT, ears, nose and throat; FA, Friedreich's ataxia.

1. Reetz K, *et al. Lancet Neurol.* 2015;14(2):174–182; 2. Content based on the speaker's clinical experience; 3. Cook A and Giunti P. *Br Med Bull.* 2017;124(1):19–30; 4. Corben LA, *et al. Orphanet J Rare Dis.* 2022;17(1):415.

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Management options for FA: Overview

Clinical management guidelines 2014 (updated in Corben LA, *et al*. 2022) were developed in collaboration with:

- International experts (clinicians and researchers)
- Patients with FA and their families

Grading of Recommendations Assessment and Evaluation (GRADE) system supplemented with:

- A summary of the literature search and review, providing indirect evidence
- Systematic collection of expert observations (structured observation form)
- Use of registry data (FA-COMS, EFACTS)

15 topic-specific chapters

130 recommendations

95 best practice statements

Symbols used to denote strength of recommendation and level of evidence

Strength of recommendation`	Symbol	Level of evidence	Symbol
Strong for intervention	↑↑	High	⊕⊕⊕⊕
Conditional for intervention	↑	Moderate	⊕⊕⊕◯
Neither intervention nor comparison	–	Low	⊕⊕◯◯
Conditional against intervention	↓	Very low	⊕◯◯◯
Strong against intervention	↓↓		

Table adapted from Corben LA, *et al.* 2022.

EFACTS, European Friedreich's Ataxia Consortium for Translational Studies; FA, Friedreich's ataxia; FA-COMS, FA Clinical Outcome Measures.
Corben LA, *et al. Orphanet J Rare Dis.* 2022;17(1):415.

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Management options for FA: Guidelines (1)

Neurological manifestations	Strength	Level of evidence
Multi-faceted rehabilitation or exercise (3 days a week at least) in ambulant patients	↑↑	+++
Computer- or video-based coordination or balance training		
Ankle and foot strengthening and stretching in combination in ambulant patients	↑↑	+
Gait aids for ambulant patients at risk of fall		
Core/spinal stability essential for functional limb movements		
Upper limb strengthening (non-ambulant) – Caution not to 'over exercise' when reliant on upper limbs to transfer	↑↑	+
Intensive speech and behavioural therapy for dysarthria	↑	++
Non-pharmacological treatment as the first option for management of spasticity	↑	++
Antimuscarinic agents/intermittent catheterisation for lower urinary tract symptoms	↑	+
Phosphodiesterase-5 inhibitors for sexual dysfunction in male patients	↑↑	+
Auditory testing	↑↑	++
Oral medication for painful peripheral neuropathy	↑	++

Table adapted from Corben LA, *et al.* 2022.

FA, Friedreich's ataxia.

Corben LA, *et al. Orphanet J Rare Dis.* 2022;17(1):415.

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Management options for FA: Guidelines (2)

Cardiac manifestations	Strength	Level of evidence
Annual ECG and echocardiogram		
24 hour holter monitoring or loop recorder for patients with palpitations or other symptoms suggesting an arrhythmia		
Anticoagulation/consideration of ablation in atrial fibrillation/atrial tachyarrhythmias	↑	+
Treatment according to American Heart Association guidelines for reduced left ventricular function	↑	+
Consider implantable devices based on cardiac and overall health status	↑	+
Coronary artery disease is as common in the normal population	↑↑	++
ECG abnormalities and Trop T elevation are common	↑↑	++
Increased incidence of pulmonary embolism	↑↑	++

Table adapted from Corben LA, *et al.* 2022.

ECG, electrocardiogram; FA, Friedreich's ataxia.

Corben LA, *et al. Orphanet J Rare Dis.* 2022;17(1):415.

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Management options for FA: Guidelines (3)

Orthopaedic manifestations	Strength	Level of evidence
Scoliosis >40 degree may be considered for surgery		
Use of foot orthotics if issues - surgery if improvement in foot alignment and/or mobility	↑	+
Consider age and ambulant status before surgery	↑	++

Endocrine manifestations	Strength	Level of evidence
Annual screening for DM and involvement of diabetes specialists for individual approach		
Insulin alone in children, insufficient evidence in adults for additional glucose lowering agents	↑	+
Screening of bone mineral density in adults	↑↑	++
Supplementation of nutritional deficiencies (e.g. calcium, vitamin D) in adults and children		

Mental health and cognition	Strength	Level of evidence
Regular monitoring and use of antidepressant/anti-anxiety medication	↑↑	++
Lifestyle changes prior or in combination	↑↑	++

Table adapted from Corben LA, *et al.* 2022.

DM, diabetes mellitus; FA, Friedreich's ataxia.
Corben LA, *et al. Orphanet J Rare Dis.* 2022;17(1):415.

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Multidisciplinary team

- Neurologist / FA specialist[1]
- General practitioner[1]
- Speech therapist[1,3]
- Physiotherapist[1,3]
- Occupational therapist[1,3]
- Endocrinologist /diabetologist[1]
- Orthopedist[1]
- Cardiologist[1]
- Psychiatrist / Psychologist[1,3]
- Ophthalmologist[3]
- Sleep doctor[2]
- Gastroenterologist[3]
- Geneticist[1]
- Urologist / Neuro-Urologist[2,3]
- Palliative care physician[3]

FA: Friedreich-Ataxie.

1. Rare Disease Advisor. Friedreich Ataxia (FA) Care Team. https://www.rarediseaseadvisor.com/hcp-resource/friedreich-ataxia-care-team (Abgerufen im Dezember 2023); 2. ERN-RND. Consensus Clinical Management Guidelines for Friedreich's ataxia. https://www.ern-rnd.eu/wp-content/uploads/2019/10/ERN-RND-Affirmed-FA-Guidelines_Final.pdf (Abgerufen im Juli 2023); 3. Ataxia UK. Management of the ataxias towards best clinical practice. Third edition. 2016. https://www.ataxia.org.uk/wp-content/uploads/2020/11/Ataxia_UK_Medical_Guidelines._Third_Edition._v3m_Dec_2016_-_updated_Sep_2019.pdf (Abgerufen im Juli 2023).

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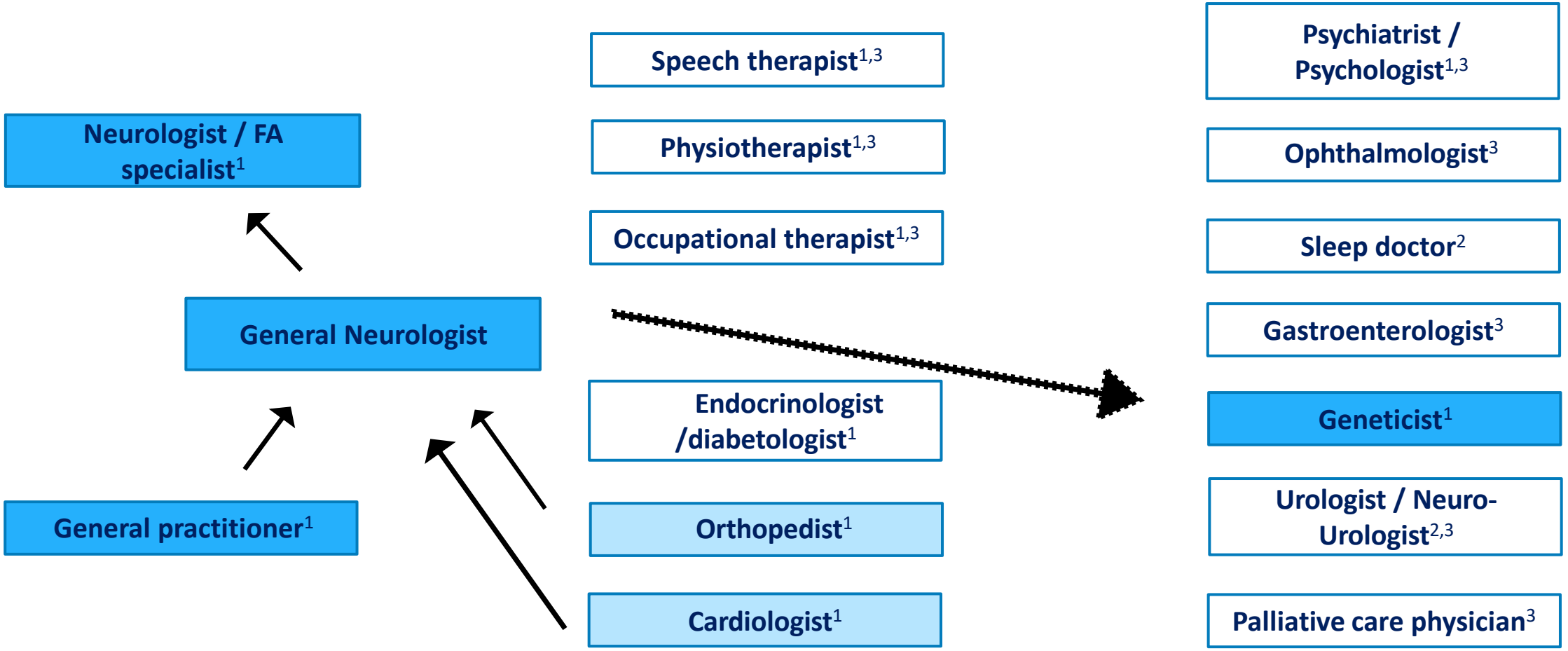
Multidisciplinary team - Diagnosis



FA: Friedreich-Ataxie.

1. Rare Disease Advisor. Friedreich Ataxia (FA) Care Team. https://www.rarediseaseadvisor.com/hcp-resource/friedreich-ataxia-care-team (Abgerufen im Dezember 2023); 2. ERN-RND. Consensus Clinical Management Guidelines for Friedreich's ataxia. https://www.ern-rnd.eu/wp-content/uploads/2019/10/ERN-RND-Affirmed-FA-Guidelines_Final.pdf (Abgerufen im Juli 2023); 3. Ataxia UK. Management of the ataxias towards best clinical practice. Third edition. 2016. https://www.ataxia.org.uk/wp-content/uploads/2020/11/Ataxia_UK_Medical_Guidelines._Third_Edition._v3m_Dec_2016_-_updated_Sep_2019.pdf (Abgerufen im Juli 2023).

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Multidisciplinary team – early disease

Neurologist / FA specialist

General practitioner[1]



Speech therapist[1,3]

Physiotherapist[1,3]

Occupational therapist[1,3]

Endocrinologist /diabetologist[1]

Orthopedist[1]

Cardiologist[1]

Psychiatrist / Psychologist[1,3]

Ophthalmologist[3]

Sleep doctor[2]

Gastroenterologist[3]

Geneticist[1]

Urologist / Neuro-Urologist[2,3]

Palliative care physician[3]

FA: Friedreich-Ataxie.

1. Rare Disease Advisor. Friedreich Ataxia (FA) Care Team. https://www.rarediseaseadvisor.com/hcp-resource/friedreich-ataxia-care-team (Abgerufen im Dezember 2023); 2. ERN-RND. Consensus Clinical Management Guidelines for Friedreich's ataxia. https://www.ern-rnd.eu/wp-content/uploads/2019/10/ERN-RND-Affirmed-FA-Guidelines_Final.pdf (Abgerufen im Juli 2023); 3. Ataxia UK. Management of the ataxias towards best clinical practice. Third edition. 2016. https://www.ataxia.org.uk/wp-content/uploads/2020/11/Ataxia_UK_Medical_Guidelines._Third_Edition._v3m_Dec_2016_-_updated_Sep_2019.pdf (Abgerufen im Juli 2023).

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Multidisciplinary team – progressive disease



- Neurologist / FA specialist
- General practitioner[1]
- Speech therapist[1,3]
- Physiotherapist[1,3]
- Occupational therapist[1,3]
- Endocrinologist /diabetologist[1]
- Orthopedist[1]
- Cardiologist[1]
- Psychiatrist / Psychologist[1,3]
- Ophthalmologist[3]
- Sleep doctor[2]
- Gastroenterologist[3]
- Geneticist[1]
- Urologist / Neuro-Urologist[2,3]
- Palliative care physician[3]

FA: Friedreich-Ataxie.

1. Rare Disease Advisor. Friedreich Ataxia (FA) Care Team. https://www.rarediseaseadvisor.com/hcp-resource/friedreich-ataxia-care-team (Abgerufen im Dezember 2023); 2. ERN-RND. Consensus Clinical Management Guidelines for Friedreich's ataxia. https://www.ern-rnd.eu/wp-content/uploads/2019/10/ERN-RND-Affirmed-FA-Guidelines_Final.pdf (Abgerufen im Juli 2023); 3. Ataxia UK. Management of the ataxias towards best clinical practice. Third edition. 2016. https://www.ataxia.org.uk/wp-content/uploads/2020/11/Ataxia_UK_Medical_Guidelines._Third_Edition._v3m_Dec_2016_-_updated_Sep_2019.pdf (Abgerufen im Juli 2023).

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Pharmacological approaches for FA

Perspectives from 30 years of research into FA[1]

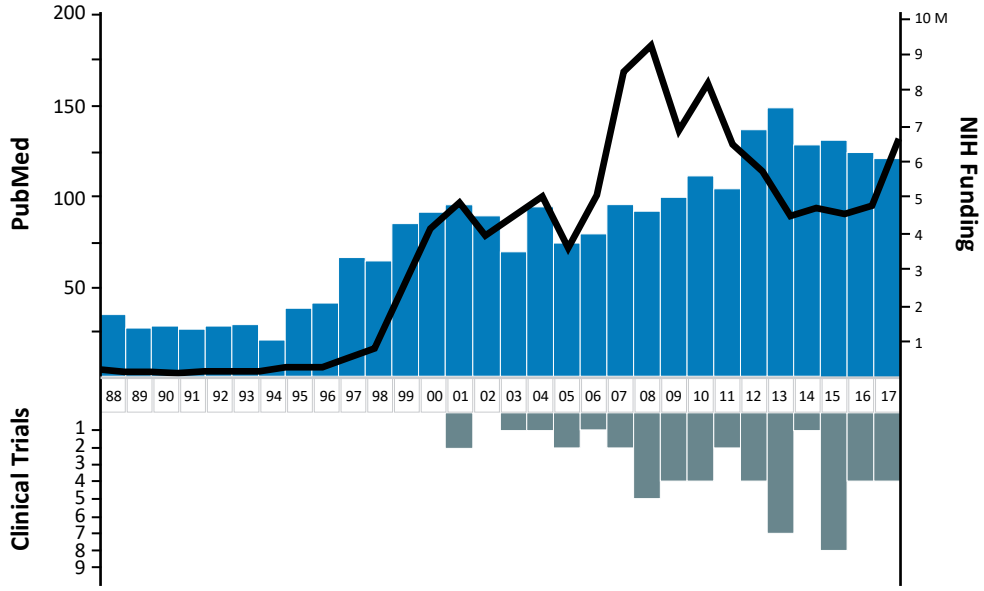
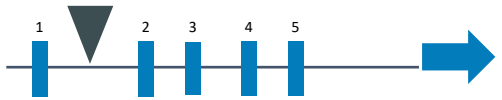


Figure adapted from Zhang S, *et al.* 2019.[1]

Therapeutic strategies in FA[2]

expanded GAA repeat in the first intron of FXN *gene*



Gene therapy

Pre-clinical[3]
Phase 1[3]

abnormal DNA conformation and/or R-Loop between arising mRNA and DNA template leading to physical blockage of transcription and/or heterochromatinisation

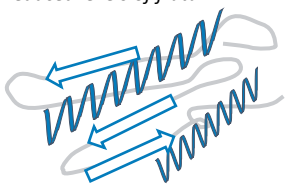


Histone deacetylase inhibitors

Antisense oligonucleotides

Pre-clinical[3]
Phase 1/2[3]

reduced levels of frataxin

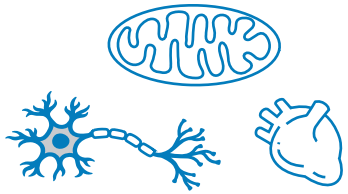


TAT-frataxin

Ubiquitination inhibitors

Phase 1/2[3]

Defective iron sulfur-cluster biogenesis, impaired oxidative phosphorylation and iron trafficking, oxidative stress



Mitochondrial function enhancers

Antioxidants

Iron chelators

Phase 2[3]
Phase 3[3]

Figure adapted from Indelicato E and Bösch S. 2017.[2]

FA, Friedreich's ataxia.

1. Zhang S, *et al. Trends Pharmacol Sci.* 2019;40(4):229–233; 2. Indelicato E and Bösch S. *Expert Opin Orphan Drugs.* 2017;6(1):57–67; 3. Content based on the speaker's clinical experience.

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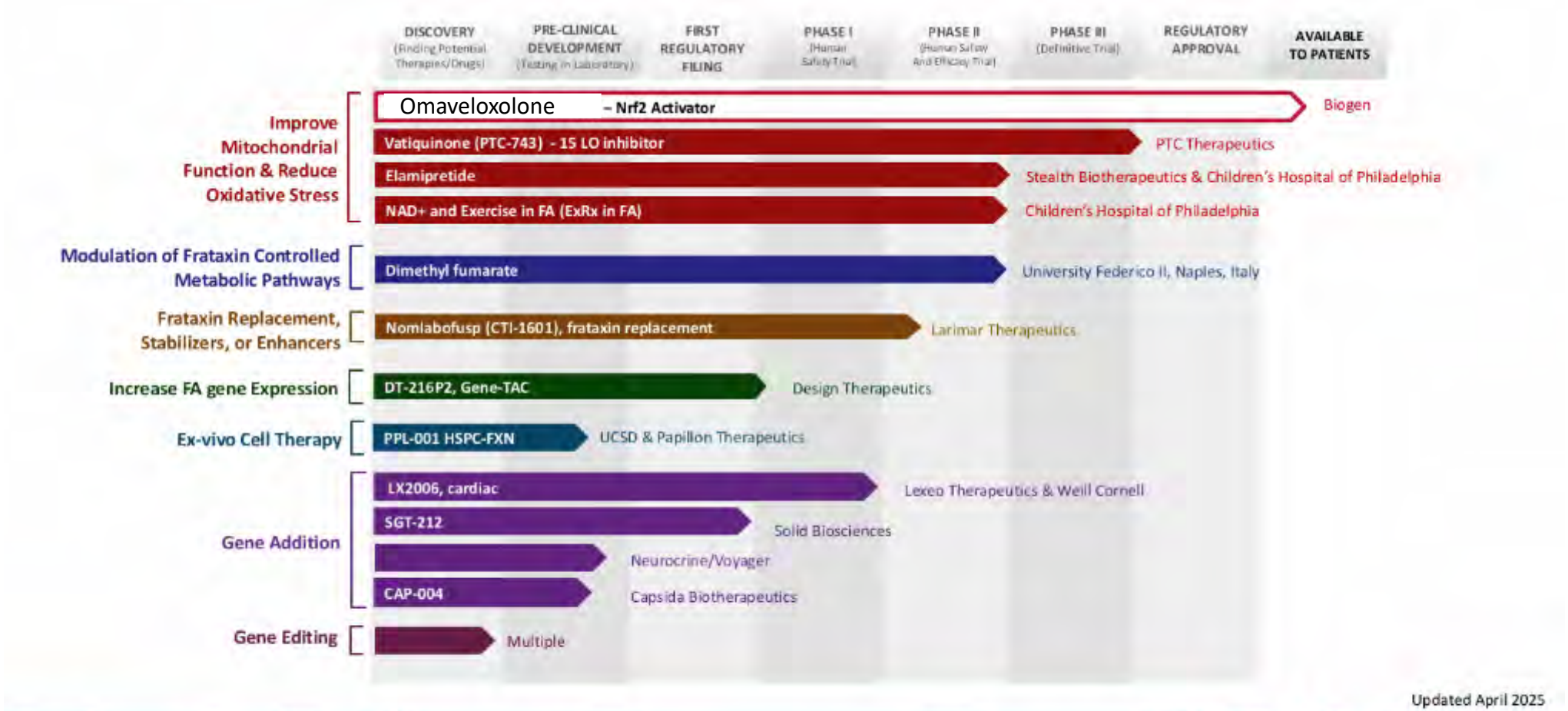
Pharmacological approaches for FA



Updated April 2025

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FARA Friedreich's Ataxia Research Alliance

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MOXIe study overview

Evaluating the safety and efficacy of omaveloxolone in patients with FA[1]

Omaveloxolone is an Nrf2 activator targeting dysfunctional mitochondrial and oxidative stress pathways[1]

Patients aged 16–40 years of age with genetically confirmed FA[2]

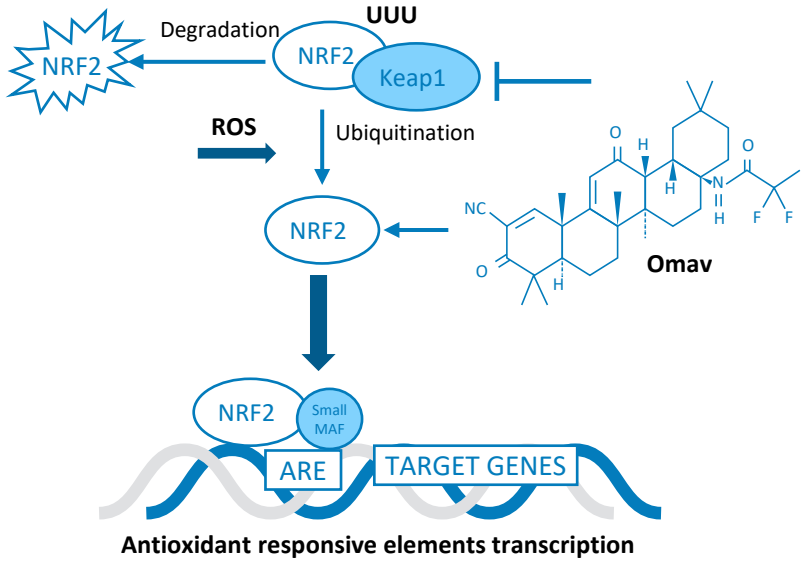

Figure adapted from Abeti R, *et al.* 2018.[5]

The MOXIe study was divided into three main parts:

Part 1

Randomised, placebo-controlled, double-blind, dose-ranging, multicentre trial to determine the optimal dose of omaveloxolone and evaluate safety over 12 weeks[1]

Part 2

Randomised, placebo-controlled, double-blind, parallel-group study to evaluate the safety and efficacy of omaveloxolone at the 150-mg dose identified in part 1 over 48 weeks[3]

OLE

Ongoing open-label extension study assessing the long-term safety and tolerability of omaveloxolone following completion of part 1 and part 2 of the MOXIe study (n=149)[3,4]

ARE, antioxidant responsive elements; FA, Friedreich's ataxia; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; OLE, open-label extension; Omav, omaveloxolone; ROS, reactive oxygen species.

1. Lynch DR, *et al. Ann Clin Transl Neurol.* 2018;6(1):15–262; 2. ClinicalTrials.gov. NCT02255435. Available at: https://clinicaltrials.gov/ct2/show/NCT02255435 (Accessed: June 2023); 3. Lynch DR, *et al. Ann Neurol.* 2021;89(2):212–225; 4. Lynch DR, *et al. Mov Disord*. 2023;38(2):313–320; 5. Abeti R. *et al. Front Cell Neurosci.* 2018;12:188.

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MOXIe study part 2: Design and endpoints

Objective:[1]

To evaluate the safety and efficacy of omaveloxolone at the 150-mg dose identified in part 1 over 48 weeks

Study design:[1]

Inclusion criteria: 16–40 years of age with genetically confirmed FA; baseline mFARS scores between 20 and 80; ability to complete maximal exercise testing on a recumbent stationary bicycle

Endpoints:[1,2]

Primary endpoint: The change from baseline in mFARS at Week 48 in the FAS (Note: Patients with severe pes cavus were excluded from the primary endpoint (FAS))

Secondary endpoint: The change in baseline at Week 48 in PGIC, CGIC, 9-HPT, T25-FW, frequency of falls, peak work during maximal testing and FA-ADL

Exclusion criteria
Uncontrolled diabetes (HbA1c > 11.0%)
B-type natriuretic peptide (BNP) level >200 pg/mL
History of clinically significant cardiac disease
Used antioxidant supplements within 14 days prior to study Day 1

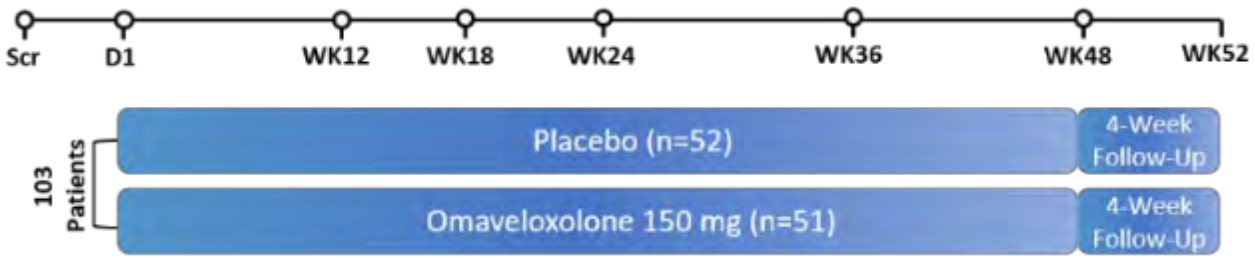

Figure from Lynch DR, *et al.* 2021.[1]

CGIC, Clinician Global Impression of Change; FA, Friedreich's ataxia; FA-ADL, Friedreich's ataxia Activities of Daily Living; FAS, full analysis set; mFARS, modified Friedreich's Ataxia Rating Scale; 9-HPT, 9-hole peg test; PGIC, Patient Global Impression of Change; T25-FW, timed 25-foot walk test.

1. Lynch DR, *et al. Ann Neurol.* 2021;89(2):212–225; 2. ClinicalTrials.gov. NCT02255435. Available at: https://clinicaltrials.gov/ct2/show/NCT02255435 (Accessed: June 2023).

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Friedreich's Ataxia Rating Scale (FARS)

- Development in 2005: SH Subramony et al. in Neurology
- Assessment of functional and neurological deficits – focus on gait and upright stability[1].
- FA specific rating scale[2], high inter-rater reliability[3]
- Time consuming compared to other rating scales [2]

Section A:



Bulbar function

Section B:



Upper limb coordination

Section C:



Lower limb coordination

Section D:



Peripheral nerve system

Section E:



Upright stability and gait

1. Subramony SH et al. Neurology. 2005;64(7):1261-1262. 2. Saute JA et al. Cerebellum. 2012;11(2):488-504. 3. Lynch DR et al. Neurology. 2006;66(11):1711-1716.

FARS vs. mFARS

		FARSn (125 pts)	mFARS (93 pts)
A1** (3) Facial atrophy A2** (3) Tongue atrophy	A3 (2) Cough A4 (3) Speech	Bulbar (11)	Bulbar – (5)
B1 (3+3) Finger-finger B2 (4+4) Nose-finger B3 (4+4) Dysmetria	B4 (3+3) Rapid movements B5 (4+4) Finger taps	Upper limb coordination (36)	Upper limb coordination (36)
C1 (4+4) Heel-shin slide C2 (4+4) Heel-shin tap		Lower limb coordination (16)	Lower limb coordination (16)
D1 (2+2) Muscle atrophy D2 (5+5) Muscle weakness D3 (2+2) Vibratory sense	D4 (2+2) Position sense D5 (2+2) Deep tendon reflexes	Peripheral nervous system (26)	
E1 (4) Sitting position E2A (4) Stance feet apart E2B (4) With eyes closed E3A (4) Stance, feet together E3B (4) With eyes closed	E4 (4) Tandem stance E5 (4) Stance, dominant foot E6 (3) Tandem walk E7 (5) Gait	Upright stability (36)	Upright stability (36)

Rummey C et al. Neurol Genet. 2019;5(6):371. Adpted from Rummey C et al. *Neurol Genet*. 2019;5(6):371.

FARSn: Friedreich's Ataxia Rating Scale neurologic examination; pts: Punkte.

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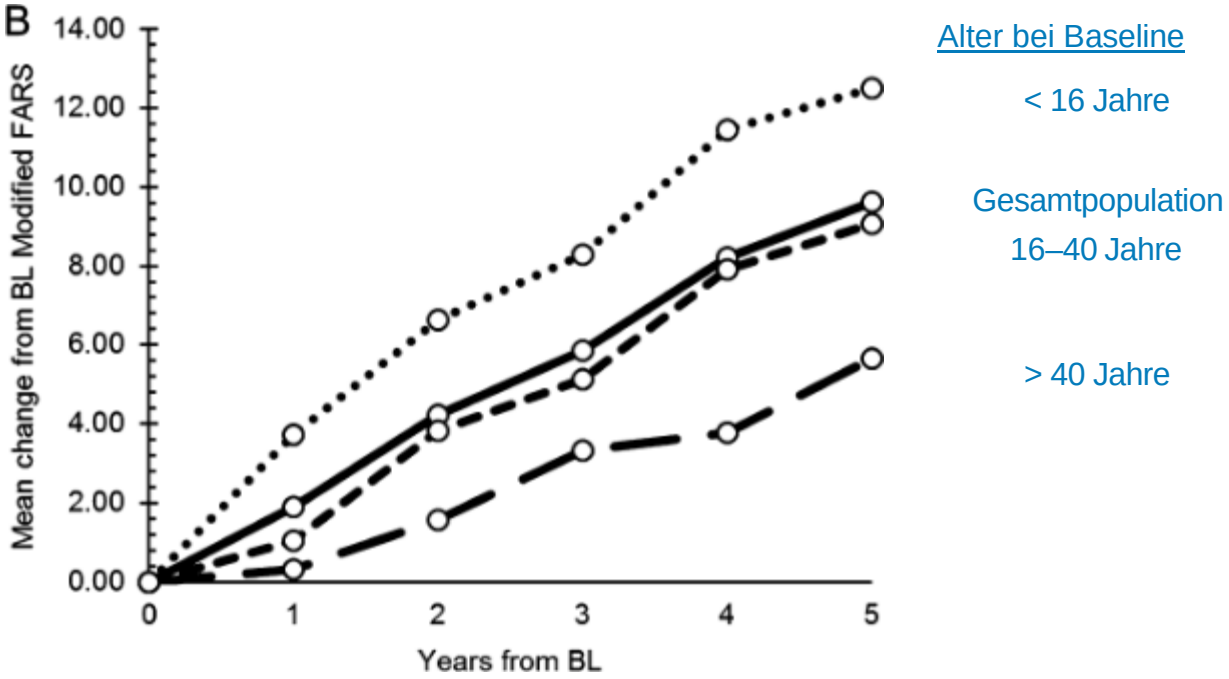
Progression mFARS-Score

Veränderung des mFARS-Scores
nach Alter bei Baseline



Untersuchung	Jahr 1	Jahr 2	Jahr 3	Jahr 4	Jahr 5
mFARS-Score	2,10 ± 6,23	4,19 ± 6,52	5,85 ± 6,97	7,80 ± 8,04	9,62 ± 8,30

Adaptiert nach Patel M et al. Ann Clin Transl Neurol. 2016;3(9):684-694

Patel M et al. Ann Clin Transl Neurol. 2016;3(9):684-694.

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MOXIe study part 2: Efficacy results (1)

Results:

Patients treated with omaveloxolone had significant **improvements in all components of mFARS (P=0.014)** compared with placebo-treated patients, **indicating that neurological function improved**

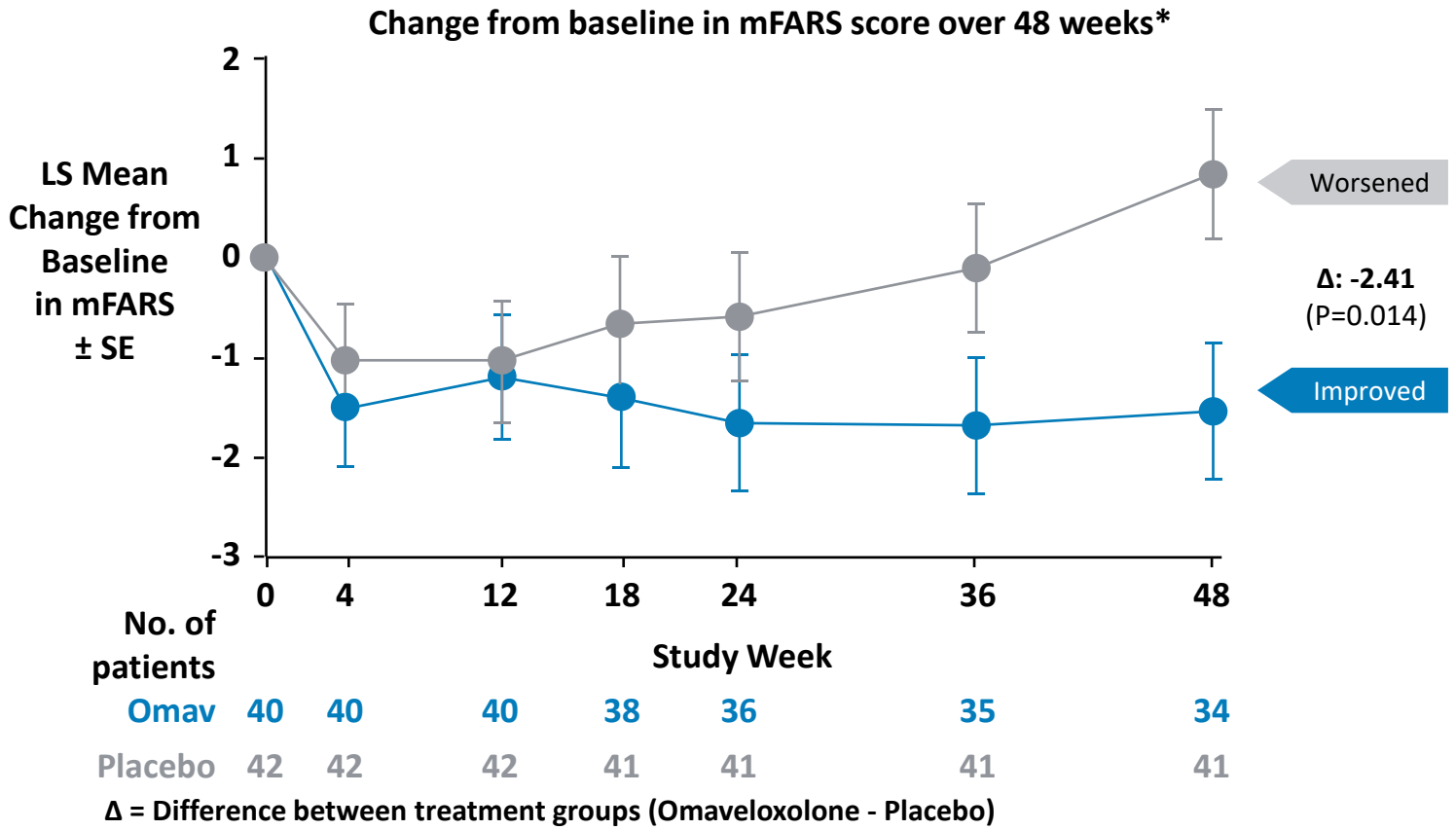

Figure adapted from Lynch DR, *et al.* 2021.

*The change from baseline in mFARS and P-value was estimated using mixed models repeated measures analysis.
LS, least square; mFARS, modified Friedreich's ataxia rating scale; SE, standard error.
Lynch DR, *et al. Ann Neurol.* 2021;89(2):212–225.

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MOXIe study part 2: Efficacy results (2)

Results:

mFARS improvements were **consistent across subgroups**, including age, sex, GAA1 repeat length and ambulatory status

Analysis* of change from baseline in mFARS score at Week 48 by subgroup in the FAS, ARP and prespecified analysis populations

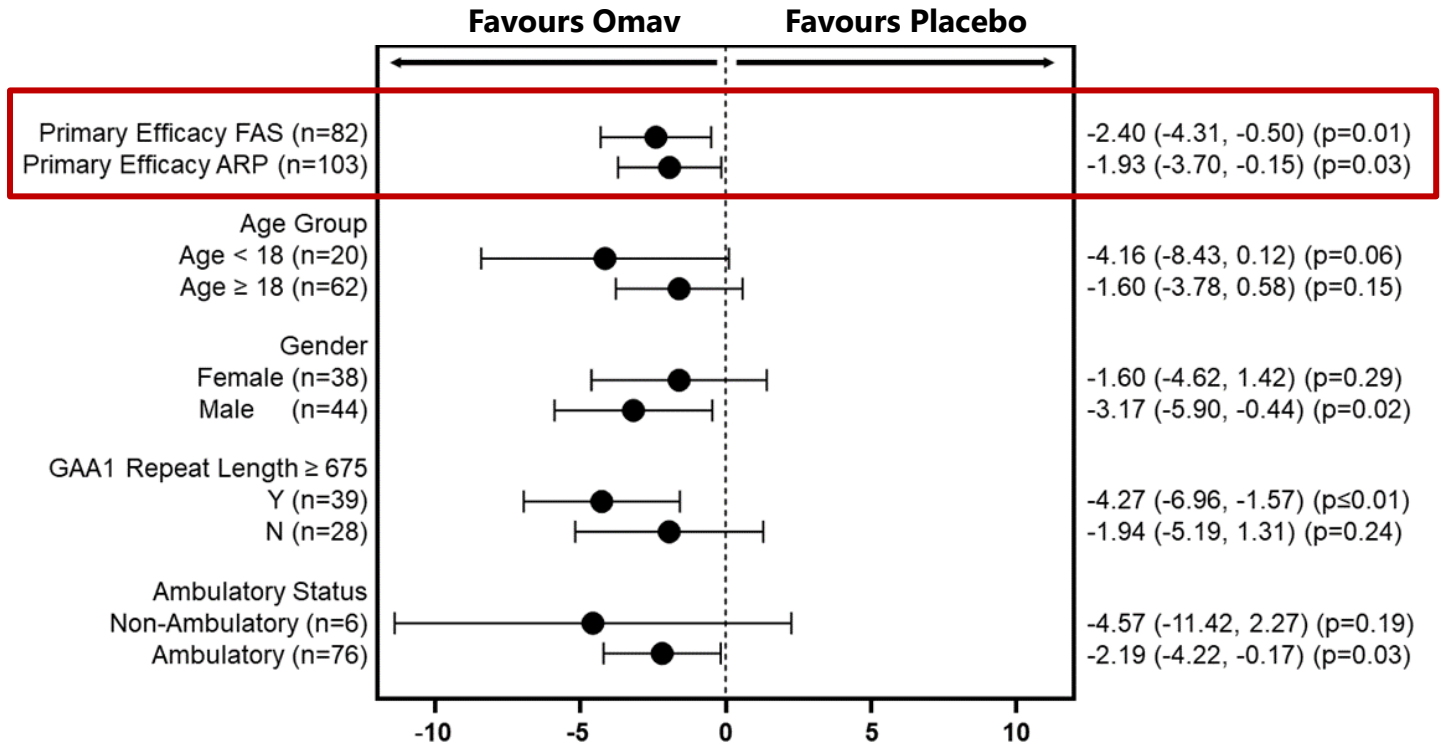

Figure from Lynch DR, *et al.* 2021.

*Change from baseline was estimated using MMRM analysis, with each P-value estimated by comparing differences between placebo and omaveloxolone groups.
ARP, all randomised patients; FAS, full analysis set; GAA1 - Guanine-Adenine-Adenine-Repeat length of the shorter allele; mFARS, modified Friedreich's ataxia rating scale; MMRM, mixed model repeated measures.
Lynch DR, *et al. Ann Neurol.* 2021;89(2):212–225.

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MOXIe study part 2: Efficacy results (3)

Results:

Secondary endpoint: **Improvement in FA-ADL** compared with placebo[1]

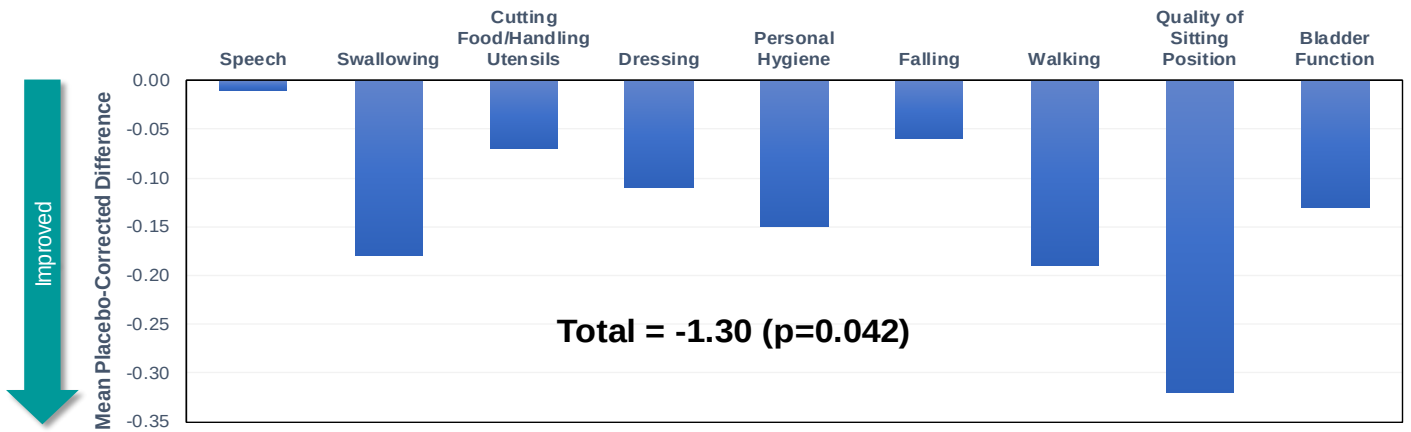

Figure from Lynch DR, *et al*. 2020.[2]

Endpoint	Omav vs baseline	Omav vs placebo
mFARS	**Improved (P=0.027)**	**Improved (P=0.014)**
PGIC	Improved	Improved
CGIC	Improved	Improved
FA-ADL	Improved	**Improved (P=0.042)**
Peak work	Improved	No Difference
9-hole peg test	No Difference	No Difference
Timed 25ft walk test	No Difference	Improved
Frequency of falls	N/A	Improved

Table from Lynch DR, *et al*. 2020.[2]

CGIC, Clinician Global Impression of Change; FA-ADL, Friedreich's ataxia Activities of Daily Living; mFARS, modified Friedreich's ataxia rating scale; PGIC, Patient Global Impression of Change.

1. Lynch DR, *et al. Ann Neurol.* 2021;89(2):212–225; 2. Lynch DR, *et al*. MOXIe: Safety and Efficacy of Omaveloxolone in Friedreich's Ataxia. Presentation at the American Academy of Neurology; 24 September 2020.

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MOXIe study part 2: Safety results

Results:

Omaveloxolone was generally **well tolerated,** with adverse events **mild-to-moderate in severity**

The most common adverse reactions were **contusion, increased ALT, nausea, increased AST and diarrhoea**

Four patients out of the 51 (8%) who received omaveloxolone discontinued treatment due to an adverse reaction compared with two discontinuations in the placebo group (4%)

Adverse reaction	Omaveloxolone, n=51 (%)	Placebo, n=52 (%)
Contusion	33	37
Headache	37	25
Upper respiratory tract infection	28	29
Excoriation	26	23
Nausea	33	14
ALT increased	37	2
Fatigue	22	14
Diarrhoea	20	10
Abdominal pain	22	6
AST increased	22	2

Table from Lynch DR, *et al.* 2021.

ALT, alanine transaminase; AST, aspartate transaminase.

Lynch DR, *et al. Ann Neurol.* 2021;89(2):212–225.

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Hepatic TEAE - Occurence

Hepatic TEAEs by time to onset; ≤12 weeks or >12 weeks

	Onset time ≤12 weeks		Onset time >12 weeks	
TEAEs, n (%)	**Omaveloxolone (n=51)**	**Placebo (n=52)**	**Omaveloxolone (n=51)**	**Placebo (n=52)**
Investigations				
ALT increase	14 (27.5)	0	0	0
AST increase	10 (19.6)	0	0	0
GGT increase	3 (5.9)	0	1 (2.0)	0
Hepatobiliary disorders				
Gall bladder disorders	0	1 (1.9)	0	0
Cholelithiasis	0	0	1 (2.0)	0
Hepatic sclerosis	0	0	1 (2.0)	0

Table adapted from Lynch DR, *et al*. 2024.

Maximum increases in ALT, AST and GGT occurred within 12 weeks of starting omaveloxolone treatment
There was no case of concomitant increases in aminotransferases and total bilirubin in the MOXIe trial

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, ɣ-glutamyl transferase; TEAE, treatment-emergent adverse event.

Lynch DR, *et al.* The MOXIe trial of omaveloxolone in Friedreich ataxia: Exploring the transient nature of treatment-emergent adverse events. Poster presented at the 10th Annual Meeting of American Academy of Neurology (AAN); 13–18 April 2024; Denver, CO, USA.

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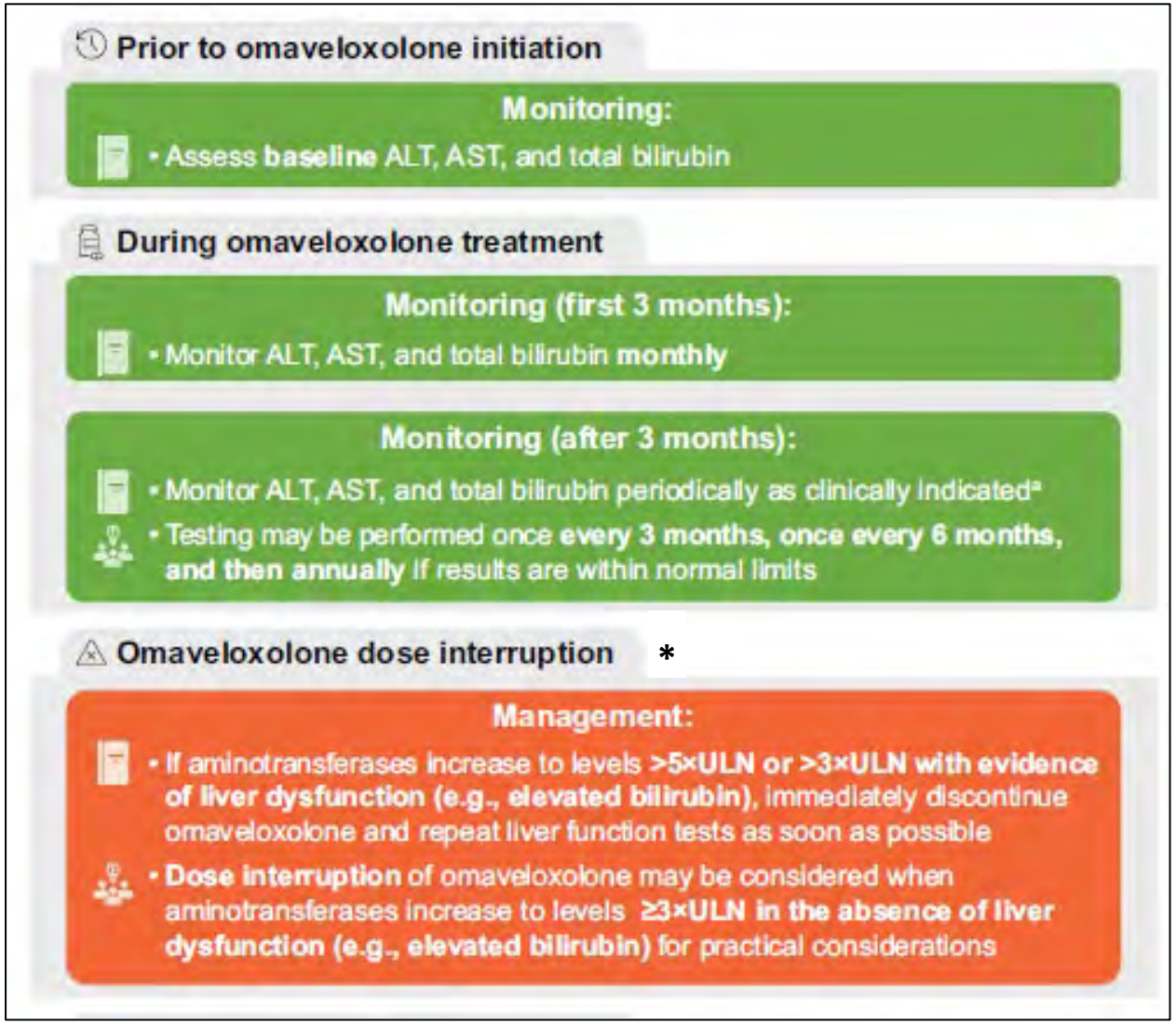
Hepatic TEAE - Management

Neurol Ther (2025) 14:1209–1227
https://doi.org/10.1007/s40120-025-00752-8

REVIEW

Managing Aminotransferase Elevations in Patients with Friedreich Ataxia Treated with Omaveloxolone: A Review and Expert Opinion on Use Considerations

Susan Perlman · Mathieu Anheim · Sylvia Boesch · James H. Lewis · David R. Lynch



ALT: Alaninaminotransferase; AST: Aspartataminotransferase; GGT: Gamma-Glutamyl-Transferase, LDL: Low density lipoprotein;
Grafik von Perlman S, et al. Neurol Ther. 2025 Aug;14(4):1209-1227.
*Das beschriebene Vorgehen stellt eine Off-Label Anwendung dar.

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Hepatic TEAE - Management

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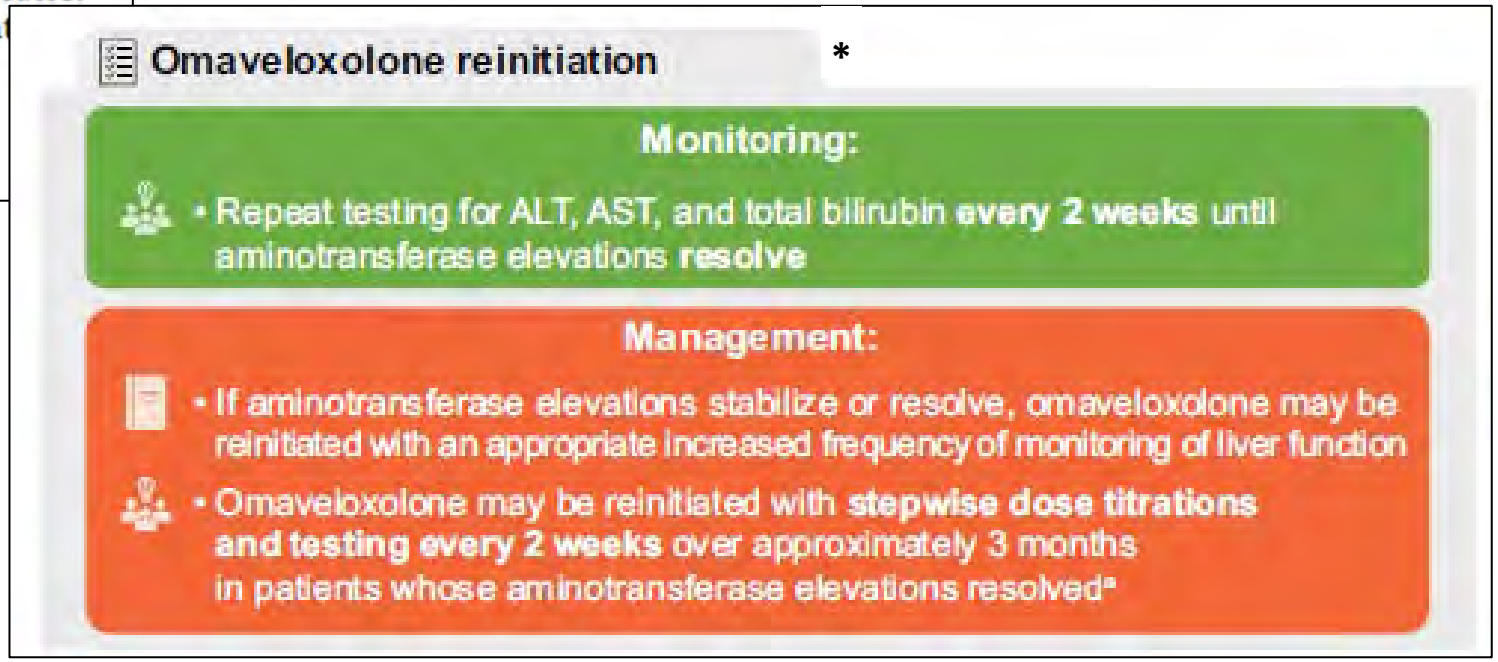
Susan Perlman · Mathieu Anheim · Sylvia Boesch · James H. Lewis · David R. Lynch



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Grafik von Perlman S, et al. Neurol Ther. 2025 Aug;14(4):1209-1227.
*Das beschriebene Vorgehen stellt eine Off-Label Anwendung dar.

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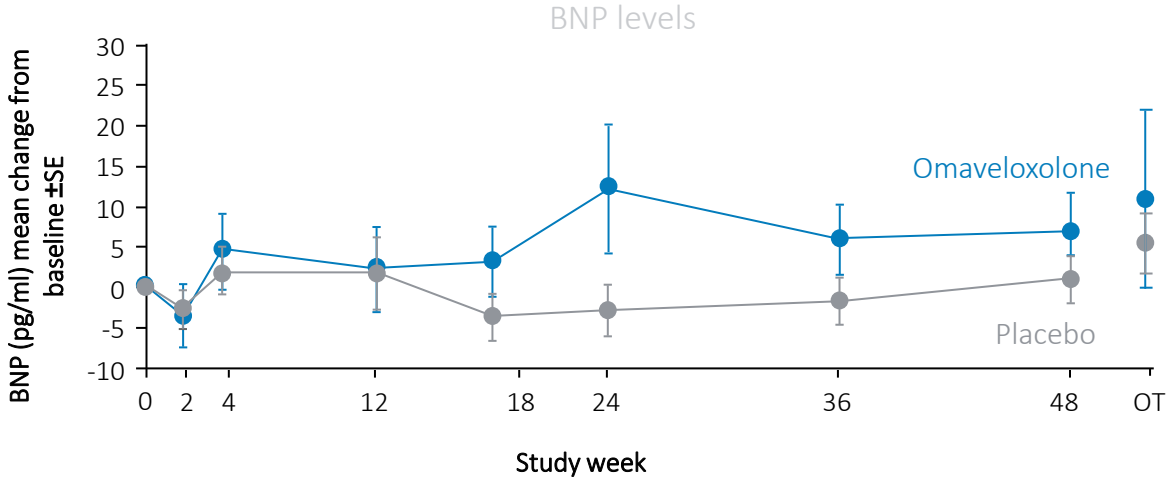
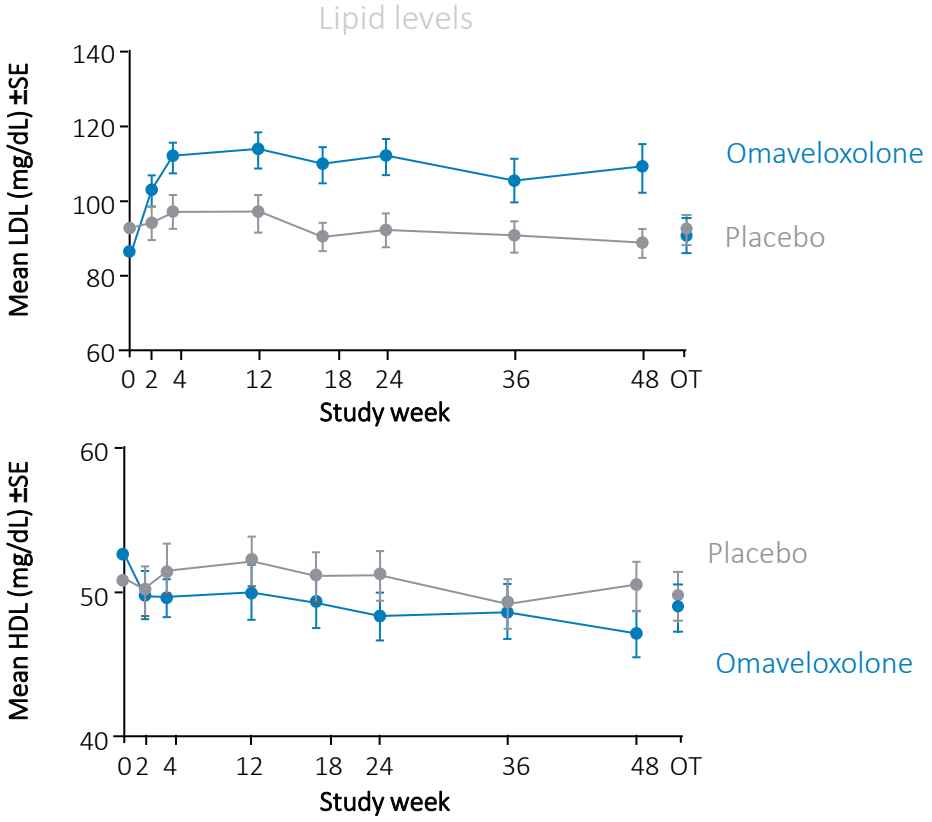
BNP und LDL levels





BNP levels were slightly elevated with omaveloxolone, but the increases were not associated with other clinical signs of fluid retention

During treatment with omaveloxolone, mean LDL levels increased and mean HDL levels decreased at Week 48 but returned to near baseline after withdrawal

Figures adapted from Subramony S, *et al.* 2023.

BNP, B-type natriuretic peptide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OT, off treatment; SE, standard error.

Subramony S, *et al.* Assessment of Cardiac Safety in Patients with Friedreich's Ataxia in the MOXIe Trial of Omaveloxolone. Poster presented at the 2023 MDA Clinical & Scientific Conference; 19–22 March 2023; Dallas, USA.

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TEAE - Duration

More common TEAEs, such as gastrointestinal disorders and liver transaminase elevations, were generally reported within the **first 12 weeks** of treatment and **decreased thereafter**

Long duration and high variability of fatigue were seen in both groups; however, **duration was numerically shorter** among those on omaveloxolone vs placebo

Events of muscle spasm and back pain were **more frequent**, with a **longer duration**, in those on omaveloxolone vs placebo

13 (25.0)

Figure adapted from Lynch DR, *et al.* 2024.

*TEAEs reported in ≥10% of participants treated with omaveloxolone and 10% greater incidence than placebo-treated participants. TEAEs are presented in order of shortest median time to first onset (top) to longest median time to first onset (bottom) in the omaveloxolone cohort.[1] Median time to onset of events was calculated from the subset of patients reporting one or more event for each TEAE.[1] †In addition to being a TEAE, fatigue is also a symptom of Friedreich ataxia, which accounted for its shorter median duration in the omaveloxolone group vs the placebo group.[1]

IQR, interquartile range; TEAE, treatment-emergent adverse event.

1. Lynch DR, *et al.* The MOXIe trial of omaveloxolone in Friedreich ataxia: Exploring the transient nature of treatment-emergent adverse events. Poster presented at the 10th Annual Meeting of American Academy of Neurology (AAN); 13–18 April 2024; Denver, CO, USA.

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MOXIe propensity-matched analysis: Overview

Objective:

To assess the value of using FA-COMS Natural History data to understand the effects of omaveloxolone in FA

Endpoints:

Primary endpoint: The change from baseline in mFARS at Year 3 for the MOXIe extension patients compared with the matched FA-COMS patients using mixed model repeated measure analysis

Study design:

A propensity-matched comparison of the data from the open-label MOXIe extension with natural history data from FA-COMS

Logistic regression was used to estimate propensity scores based on multiple covariates: **sex, baseline age, age of onset, baseline mFARS score and baseline gait score.** Selection of covariates was based on clinical relevance and availability

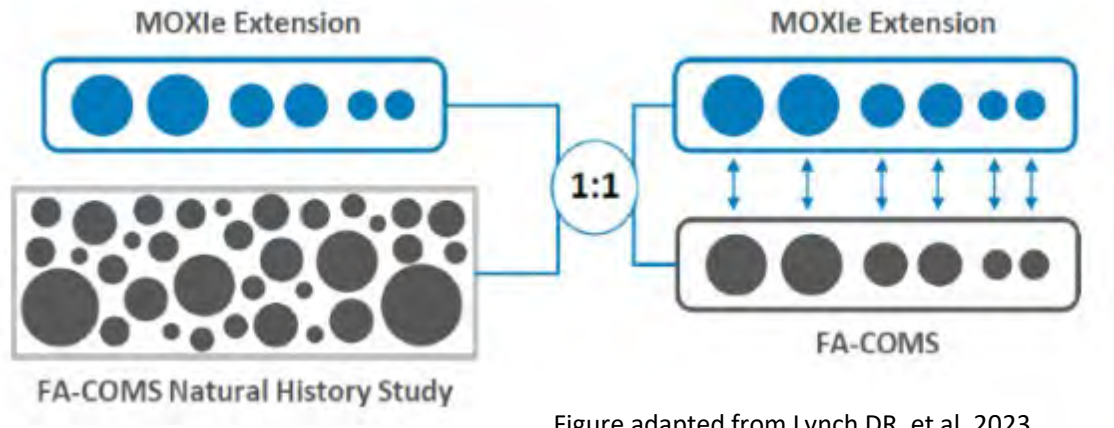

Figure adapted from Lynch DR, et al. 2023

FA, Friedreich's ataxia; FA-COMS, Friedreich's ataxia Clinical Outcome Measures Study; mFARS, modified Friedreich's ataxia rating scale.
Lynch DR, *et al.* Ann Clin Transl Neurol 2023

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MOXIe propensity-matched analysis: Results

Results:

Data from the MOXIe extension, which includes patients from both part 1 and part 2, show that omaveloxolone provides a **persistent benefit over 3 years when compared with an untreated matched cohort from FA-COMS**

In the primary pooled population by Year 3, mFARS scores for patients in the FA-COMS matched set progressed 6.6 points, whereas they progressed 3 points for patients treated with omaveloxolone (P=0.0001). The **progression in mFARS was slowed by 55% with omaveloxolone treatment**

Demographics and baseline characteristics for primary pooled population

Characteristic	Statistic	Matched FA-COMS (n=136)	MOXIe extension (n=136)
Age (years)	Mean (SD)	26.2 (13.72)	26.6 (7.26)
Age at FA onset	Mean (SD)	15.2 (10.48)	15.5 (5.30)
Sex, Female	n (%)	70 (51.5)	70 (51.5)
mFARS	Mean (SD)	41.0 (16.10)	42.2 (12.60)
Gait	Mean (SD)	2.7 (1.69)	2.8 (1.36)

Table adapted from Lynch DR, *et al.* 2022.

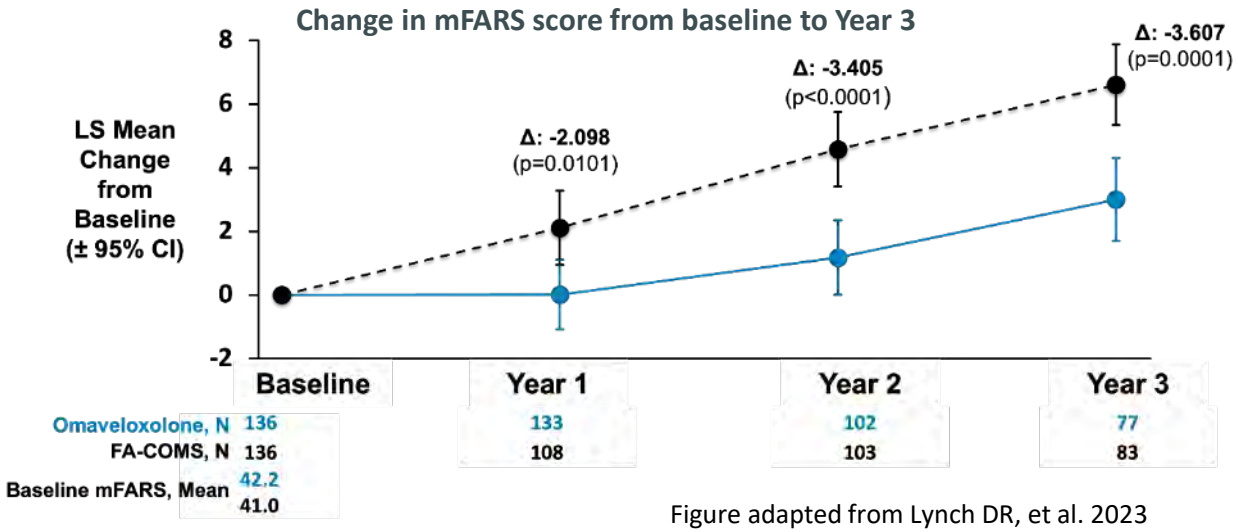

Figure adapted from Lynch DR, et al. 2023

CI, confidence interval; FA, Friedreich's ataxia; FA-COMS, Friedreich's Ataxia Clinical Outcome Measures Study; LS, least square; mFARS, modified Friedreich's ataxia rating scale; SD, standard deviation.
Lynch DR, *et al.* Ann Clin Transl Neurol 2023

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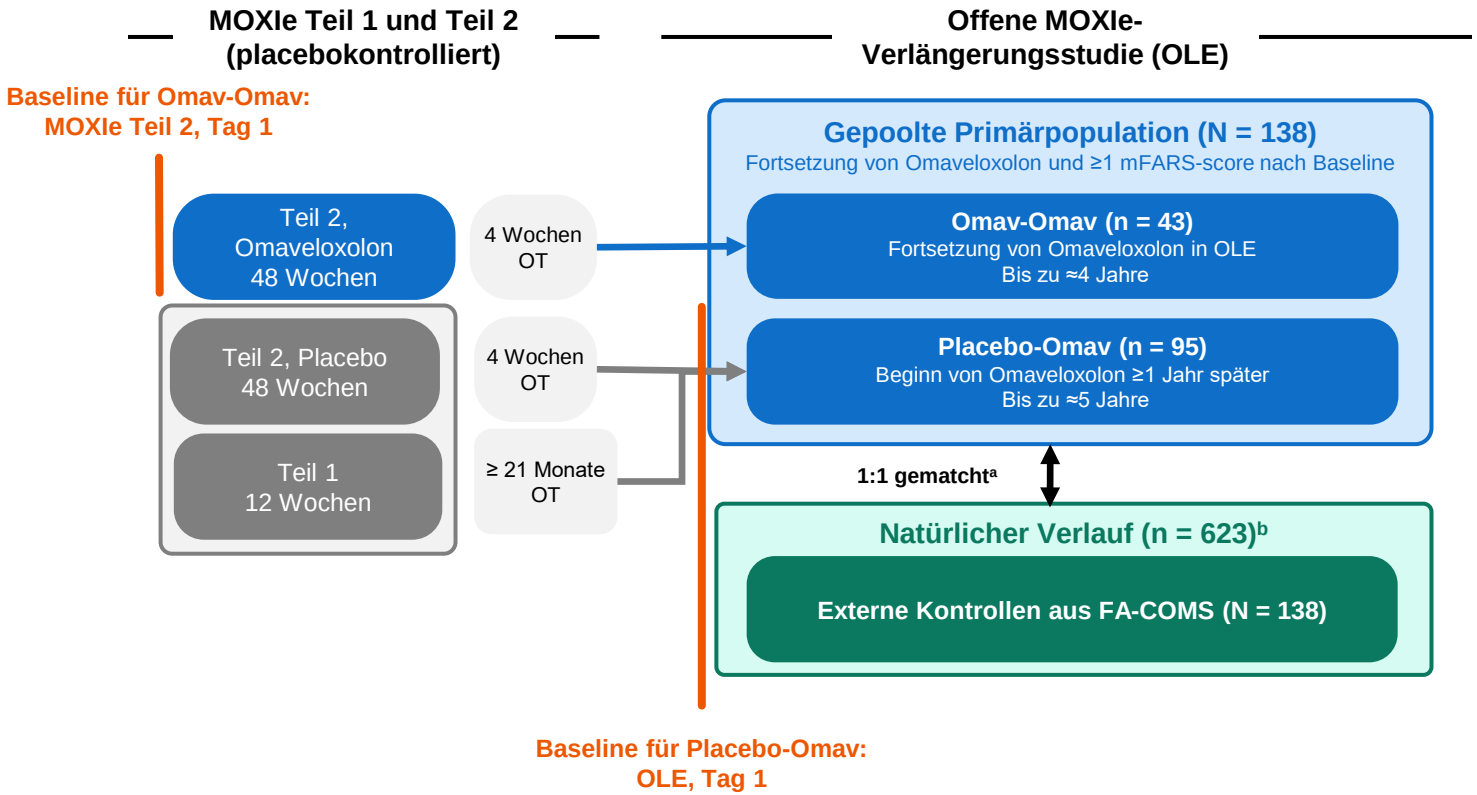
MOXIe propensity-matched analysis 5-year data[1]

Studiendesign der Propensity-Score-Matching-Analyse über 5 Jahre: Gepoolte Primärpopulation



FA: Friedreich-Ataxie; **FA-COMS:** FA Clinical Outcome Measures; **OLE:** Open-label extension; **Omav:** Omaveloxolon; **OT:** Ohne Therapie, **a** Für die Bestimmung der Propensity-Scores für das 1:1-Matching wurden folgende Kovariaten verwendet: Alter zu Baseline, Alter bei Beginn der FA, Geschlecht, Gait-Score zu Baseline und mFARS-Score zu Baseline.
b Patienten, die die Auswahlkriterien für das Matching erfüllten.

1. Nachbauer et al., Poster 234 Annual Congress of the World Muscle Society (WMS) 2025 | Vienna, Austria | October 7-11, 2025

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MOXIe propensity-matched analysis 5-year data[1]

- Die Baseline-Charakteristika zwischen den Gruppen waren ausgeglichen
- Patienten in der gepoolten Omaveloxolon-Gruppe wiesen etwas höhere mFARS-Baseline-Scores auf als die gematchten Kontrollen.

Baseline-Charakteristika:
Gepoolte Primärpopulation und gematchte FA-COMS

	Gepoolte Population (N = 138)	Gematchte FA-COMS (N = 138)
Weiblich, n (%)	70 (50,7)	70 (50,7)
Mittleres Alter, Jahre (SD)	26,2 (7,37)	25,5 (13,87)
Mittleres Alter bei Beginn der FA, Jahre (SD)	15,4 (5,30)	15,0 (9,92)
Mittlerer mFARS-Score (SD)	42,23 (12,020)	39,83 (17,220)
Mittlerer Gang-Score (SD)	2,75 (1,361)	2,54 (1,644)

FA: Friedreich-Ataxie; **FA-COMS:** FA Clinical Outcome Measures; **mFARS:** modified Friedreich Ataxia Rating Scale; **SD:** Standardabweichung

1. Nachbauer et al., Poster 234 Annual Congress of the World Muscle Society (WMS) 2025 | Vienna, Austria | October 7-11, 2025

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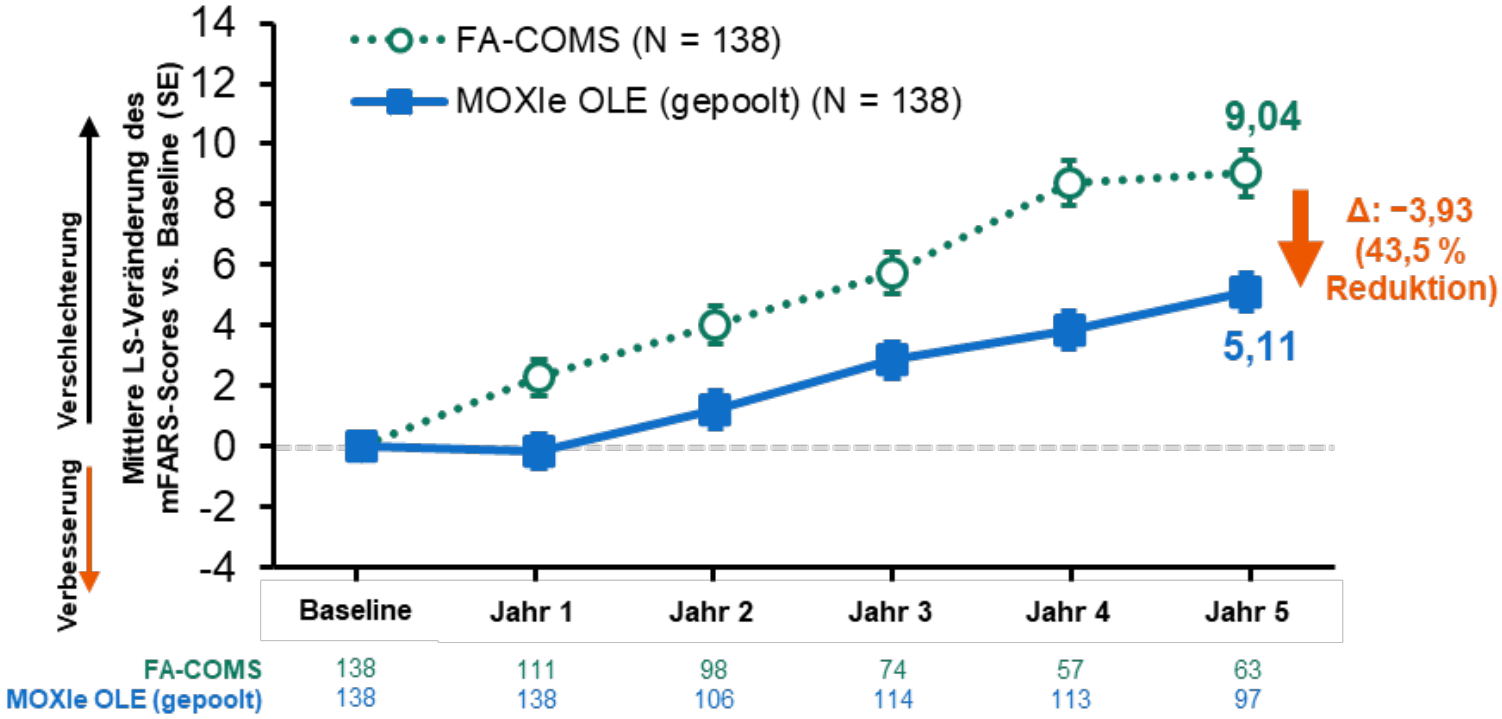
MOXIe propensity-matched analysis 5-year data[1]

- Nach 5 Jahren zeigte die gepoolte Primärpopulation (n = 97) eine geringere Progression des mFARS-Scores als die gematchten FA-COMS-Kontrollen (n = 63)
→ 5,11 vs. 9,04 Punkte;
Differenz: −3,93; p = 0,0001

- Und eine langsamere jährliche Progression (1,02 vs. 1,81 mFARS-Punkte/Jahr)

Veränderung des mFARS-Scores seit Baseline über 5 Jahre: Gepoolte Primärpopulation und gematchte FA-COMS[a]



FA: Friedreich-Ataxie; **FA-COMS:** FA Clinical Outcome Measures; **LS:** Least squares; **mFARS:** modified Friedreich Ataxia Rating Scale; **MMRM:** Gemischtes Modell mit wiederholten Messungen; **OLE:** Open-label extension; **Omav:** Omaveloxolon; **SE:** Standardfehler
Δ = Differenz der Veränderung des mFARS-Scores seit Baseline zwischen MOXIe OLE und gematchten FA-COMS-Patienten
a MMRM. Baseline war der Beginn der Omaveloxolon-Gabe (Tag 1 von MOXIe Teil 2 für Omav-Omav bzw. Tag 1 der OLE für Placebo-Omav).
1. Nachbauer et al., Poster 234 Annual Congress of the World Muscle Society (WMS) 2025 | Vienna, Austria | October 7-11, 2025

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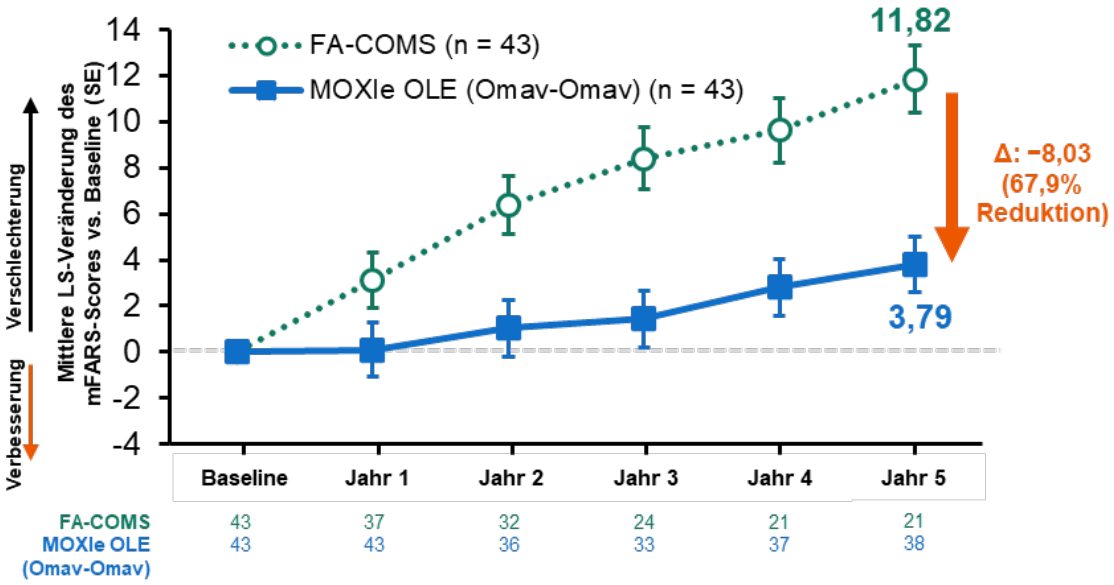
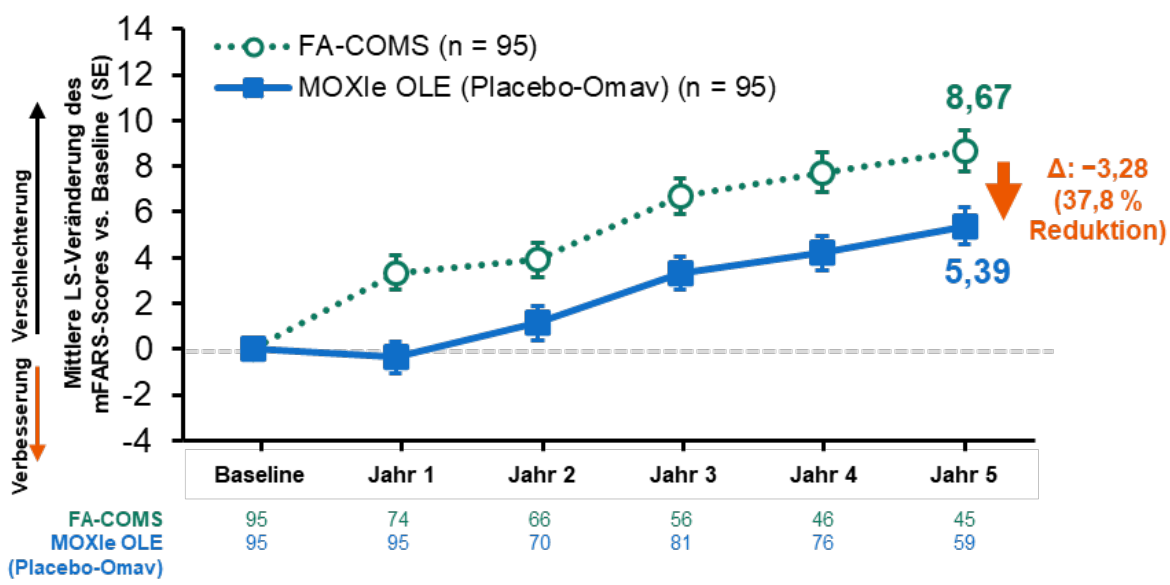
MOXIe propensity-matched analysis 5-year data[1]

Veränderung des mFARS-Scores Omav-Omav und gematchte FA-COMS[a]



Veränderung des mFARS-Scores Placebo-Omav und gematchte FA-COMS[a]



FA: Friedreich-Ataxie; **FA-COMS:** FA Clinical Outcome Measures; **LS:** Least squares; **mFARS:** modified Friedreich Ataxia Rating Scale; **MMRM:** Gemischtes Modell mit wiederholten Messungen; **OLE:** Open-label extension; **Omav:** Omaveloxolon; **SE:** Standardfehler

Δ = Differenz der Veränderung des mFARS-Scores seit Baseline zwischen MOXIe OLE und gematchten FA-COMS-Patienten

a MMRM. Baseline war der Beginn der Omaveloxolon-Gabe (Tag 1 von MOXIe Teil 2 für Omav-Omav bzw. Tag 1 der OLE für Placebo-Omav).

1. Nachbauer et al., Poster 234 Annual Congress of the World Muscle Society (WMS) 2025 | Vienna, Austria | October 7-11, 2025

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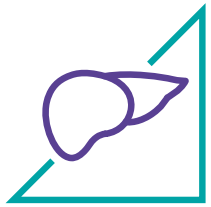
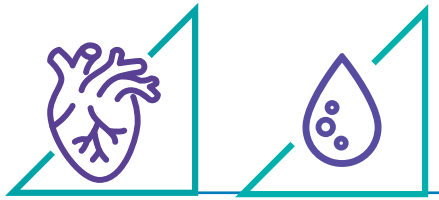
Omaveloxolon Therapie - Monitoring

	Baseline	month 1	month 2	month 3	month 4-11	month 12
Lab	✓	✓	✓	✓	routine	✓
mFARS/SARA	✓			✓		✓
ECG	✓					✓
Echo	✓					✓

Untersuchung	Vor Therapiebeginn	Während der Therapie
 **ALT, AST und Bilirubin**	✓	✓ Erste 3 Monate: monatlich Danach: in regelmäßigen Abständen, wie klinisch erforderlich
 **Lipidwerte / BNP**	✓	✓ In regelmäßigen Abständen

Monitoring Vorgehen basierend auf Skyclarys™ Fachinformation März 2026 und eigener Expertise des Referenten.

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Omaveloxolon Therapie - Monitoring

A) Appendicular and B) Axial, percentage of total scores by functional disease stage

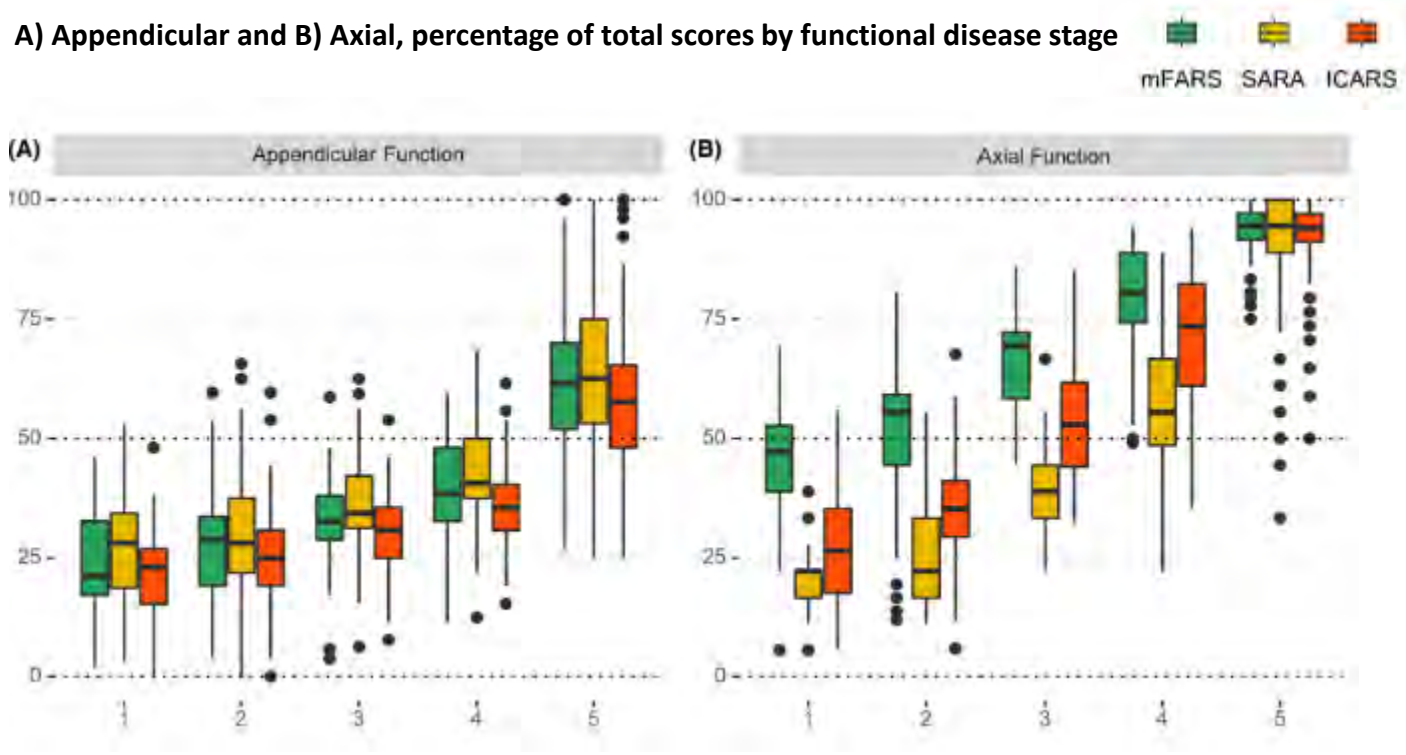
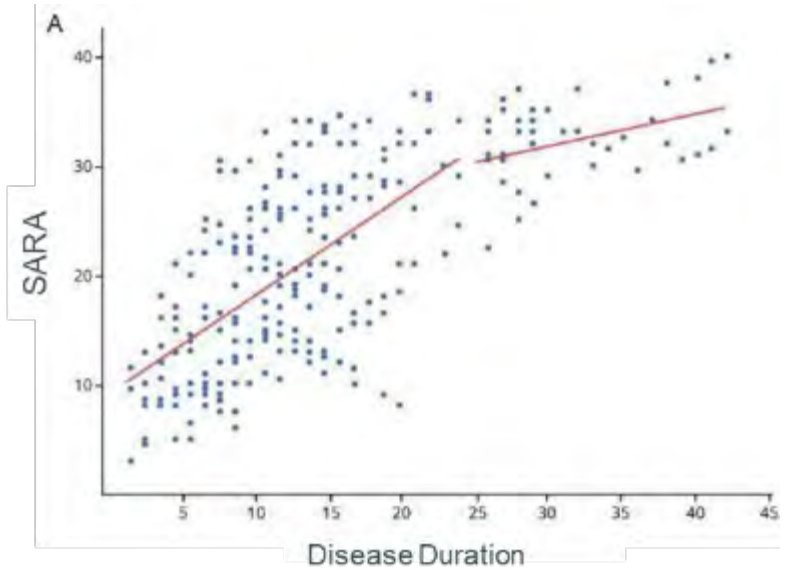


Figure from Rummey C, *et al*. 2022.

ICARS (1997)[1,4]	FARS (2005)[1,4]	SARA (2006)[1,4]
International Cooperative Ataxia Rating Scale (ICARS) 19 Items	Friedreich's Ataxia Rating Scale (FARS) 5 domains	Scale for Assessment and Rating of Ataxia (SARA) 8 Items
0–100[1,2]	0–125[1]	0–40[1]
21,3 ± 7,0 min[1]	< 30 min[1]	14,2 ± 7,5 min[1]



FA, Friedreich's ataxia; ICARS, International Cooperative Ataxia Rating Scale; mFARS, modified Friedreich's Ataxia Rating Scale; SARA, Scale for the Assessment and Rating of Ataxia.

1. Rummey C, et al. Annals of Clinical and Translational Neurology. 2020;7(9):1708–1712; 2. Lynch DR, et al. Ann Neurol. 2021;89(2):212–225; 3. Rummey C, et al. Annals of Clinical and Translational Neurology. 2022;9(12):2041–2046.
2. Pandolfo M. Neurol Genet. 2020;6(3):6e415.
3. Reetz K et al. Lancet Neurol. 2021;20(5):362-372
4. Bürk K et all. Ataxia Scales for the Clinical Evaluation, 2023 pp 493–500

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Zusammenfassung

- Die Friedreich-Ataxie ist eine **“Multisystem”- Krankheit** mit neurologischen und nicht-neurologischen Manifestationen, sowie **unterschiedliche klinischen Phänotypen**.

- Eine **kontinuierliche multidisziplinäre Behandlung** mit einem **patientenspezifischen Ansatz** ist entscheidend in der Betreuung von Friedreich-Ataxie Patienten[1].

- **Zahlreiche pharmakologische Substanzen, basierend auf verschiedenen pathophysiologischen Ansätzen**, sind aktuell in Entwicklung oder in klinischer Prüfung[1].
  - Die Kombination verschiedener Therapieansätze könnte eine entscheidende Rolle in der zukünftigen FA-Therapie spielen[2].
- Omaveloxolon zeigte einen signifikanten Unterschied im mFARS in einer placebo-kontrollierten Studie[3].
- In **Europa** besteht eine Zulassung seit Februar 2024 zur Behandlung der Friedreich-Ataxie bei Erwachsenen und Jugendlichen ab 16 Jahren[4].

FA, Friedreich’s ataxia; mFARS, modified Friedreich’s ataxia rating scale.

1. FARA. Research Pipeline. Available at: https://www.curefa.org/research/research-pipeline (Accessed: June 2023); 2. Expertenmeinung, 3. Lynch DR, *et al. Ann Neurol.* 2021;89(2):212–225., 4. SKYCLARYS™ Fachinformation Stand März 2026

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