Friedreich's Ataxia Research update

Dr Julie Greenfield

Head of Research

27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

ATAXIA

Overview

Ataxia UK activities and the process of research

Developments in new treatments

Opportunities to take part in research in the UK

Ataxia UK activities and the process of research

27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

Ataxia UK research activities

Funding Research

2023 Impact Report
Every £1 Ataxia UK spent on research projects raised £5 in further funding for ataxia research

27th & 28th September 2024
VIRTUAL ANNUAL CONFERENCE

Research events

International Congress for Ataxia Research
ICAR
ATAXIA · ATAXIA GLOBAL INITIATIVE · FARA · NAF National Ataxia Foundation

SAVE THE DATE: ICAR 2024
November 12-15, 2024 • London, UK

Meeting for UK researchers
Sep 2023

Ataxia UK research activities

Ataxia UK links researchers and ataxia community

- Recruitment to studies
- Engagement in research
- Patient voice

Working with pharma and biotech companies

- Encourage involvement in ataxia research
- Assist with drug development programmes
- Collect useful information

Ataxia UK is engaged in all stages of research

27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

Process of clinical trials

Preclinical several years

- Test drug in cells and/or animal models
- Dosing and safety before giving to humans

Phase 1 Several months

- Safety of drug
- How the body processes drug and its effect on body
- Information on dosing

Phase II Several months to 2 years

- Potential risks and benefits
- Does drug work in people who have the condition?
- Continues to study safety

Phase III 1 to 4 years

- Potential risk and benefits compared to no treatment or existing treatment
- Typically, people are given the drug or placebo
- Continues to study safety and whether drug works in more people

*for rare diseases such as ataxia, the numbers of people in trials are much smaller and the different phases of trial might be combined

Next step after a successful clinical trial

Step 1: a treatment needs to get a **licence** from a **regulatory agency** before it can be made available

Step 2: In the UK, **different bodies** decide whether the **NHS will provide** the treatment

UK: MHRA
Europe: EMA
US: FDA

England, Wales, NI: NICE
Scotland: SMC

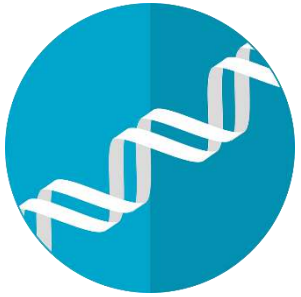
Developments in new treatments

27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

The aim of FA research

A mistake in the frataxin gene



Genetic approaches to correct or replace frataxin gene

A reduction in the amount of frataxin protein

Frataxin protein

Increase the amount of the frataxin protein

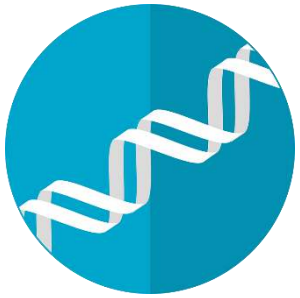
Disrupted processes within cells

- **Oxidative stress**
- **↑ iron in mitochondria**
- **Cell damage**
- **Disrupted mitochondrial function and ↓ energy production**

Target the disrupted cellular processes

27th & 28th September 2024
VIRTUAL ANNUAL CONFERENCE

A mistake in the frataxin gene



A reduction in the amount of frataxin protein

Frataxin protein

Disrupted processes within cells

- **Oxidative stress**
- **↑ iron in mitochondria**
- **Cell damage**
- **Disrupted mitochondrial function and ↓ energy production**

Developments in new treatments: Genetic approaches

Genetic approaches in FA

Design Therapeutics

- **DT-216** designed to target mutation in frataxin gene
- December 2022 and August 2023 – Phase 1 clinical trial showed **promising initial results**
- Conducted nonclinical studies to **improve formulation**
- March 2024: new formulation showed improved absorption and safety
- Next **phase I trial** expected in **2025**

LEXEO Therapeutics

- Gene therapy **LX2006** designed to transfer frataxin gene to heart cells
- **Phase I/II clinical trial -**SUNRISE-FA
- 3 ascending dose cohorts
- June 2023: 1st cohort **tolerated dose well**
- March 2024: 2nd cohort results show increase in frataxin after 3 months
- July 2024: Interim data showed clinically meaningful improvements across multiple cardiac markers of hypertrophy, which is a key hallmark of FA cardiomyopathy.

Genetic approaches in FA

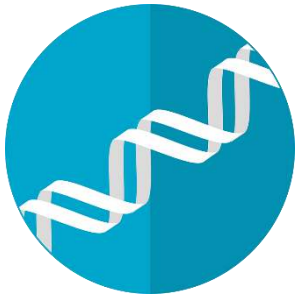
Many research groups and companies are conducting preclinical research for gene therapies for FA

Recent updates March 2024

Prime medicine – gene editing targeting GAA repeats, promising preclinical results, aim to develop lead drug in 2024.

Voyager Therapeutics and Neuroendocrine biosciences - gene therapy replacement of frataxin gene, delivered via capsid. Selected lead candidate drug, expect human trials in 2025.

A mistake in the frataxin gene



A reduction in the amount of frataxin protein

↓ **Frataxin protein**

Disrupted processes within cells

- **Oxidative stress**
- **↑ iron in mitochondria**
- **Cell damage**
- **Disrupted mitochondrial function and ↓ energy production**

Developments in new treatments:

Increase frataxin protein

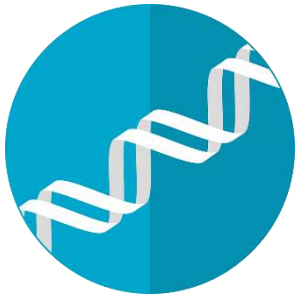
Increase frataxin protein

Larimar Therapeutics

- Protein replacement therapy
- **CTI-1601** delivers frataxin to the mitochondria

- Phase II - ascending dose trial
- Feb 2024: positive topline results, well tolerated for both doses, increases in frataxin levels at day 14
- Open label trial is ongoing, with interim results expected at the end of 2024.

A mistake in the frataxin gene



A reduction in the amount of frataxin protein

↓ **Frataxin protein**

Disrupted processes within cells

- **Oxidative stress**
- **↑ iron in mitochondria**
- **Cell damage**
- **Disrupted mitochondrial function and ↓ energy production**

Developments in new treatments:

Target disrupted processes

Omaveloxolone

Generic name: Omaveloxolone -> 'Omav'

Brand name: SYKCLARYS ®

- Developed by Reata Pharmaceuticals
- Now owned by Biogen (September 2023)
- **First approved drug for FA**
- **Slows progression**
- FDA approval for adults aged 16 years and over Feb 2023
- EMA approval Feb 2024

Omaveloxolone in the UK

- The UK regulatory process consists of two stages:
  - **MHRA** decide whether to approve the drug
  - **NICE** (or **SMC** in Scotland) decide whether the drug will be available on the NHS
- Biogen intends to submit to the **MHRA** in Q4 of 2024. We anticipate we will know the outcome of this decision: April-June 2025).
- Biogen is working on evidence submission to **NICE**. Ataxia UK also very involved in this process. Scoping workshop – 30th Aug
- Once the dossier has been prepared for NICE Biogen will adapt it and also submit it to the **SMC**.

27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

Keep updated with Omav news at www.ataxia.org.uk/omav-updates/

We want to hear from you

If you or someone you know has a confirmed diagnosis of FA and are aged 16 and above, <u>we want to hear from you</u>

- As part of the NICE evaluation process, we are inviting adults with FA to share case studies of the impact of FA on their lives.

If you or someone you know took part in the Omaveloxolone clinical trial in the UK, <u>we want to hear from you</u>

- We are collecting feedback from people who have taken or are taking Omaveloxolone for their FA, to support the NICE evaluation process.

Email research@ataxia.org.uk and we will send you questions.

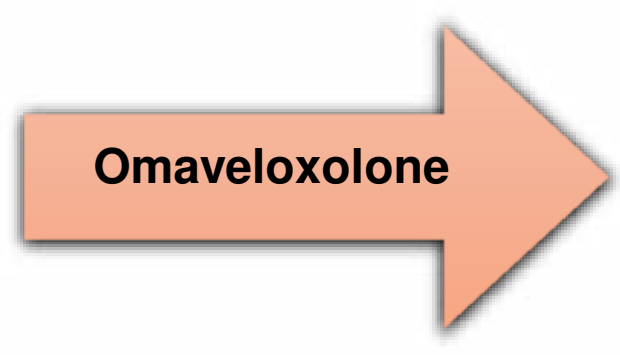
27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

What does Omaveloxolone do?

In FA, reduced frataxin leads to:

- Oxidative stress
- Disrupted mitochondria function
- Reduced energy production



Nrf2 transcription factor activator

In preclinical models of FA:

- **Nrf2 activator/ anti-oxidant**
- **↑ mitochondrial function**
- **↑ energy production**

Reduces the damage caused by low frataxin levels

27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

Omaveloxolone is a disease-modifying treatment for FA

The MOXIe trial

The MOXIe trial was multi-centre clinical trial to test Omaveloxolone. The London Ataxia Centre was the UK trial site.

Part I: Good safety and **best dose** for part II, Improvement in mFARS

69 participants
3:1 Omav: placebo
12 weeks
Results 2018

Part II: Single dose of 150mg: confirmed safety and **significant improvement** in **mFARS**

103 participants
1:1 Omav: Placebo
48 weeks
Results 2019

Open-label extension: Further evidence of **positive effect**

92 participants
All on Omav
Eligible from Part I and II
Results 2021

Positive comparison to natural history data
OMAV slows progression

27th & 28th September 2024
VIRTUAL ANNUAL CONFERENCE

Will Omav be approved in children?

Trials are needed to see if Omav is safe for children under 16

- Phase I Study US single centre
  Started in summer 2024
  To assess **safety and tolerability**
  Estimated 20 participants
  2-15 years – single dose study followed by open label extension
- Global paediatric trial to follow

Vatiquinone

PTC Therapeutics - Phase III trial MOVE-FA

May 2023 results: **No significant change in overall mFARS score**
But did see **meaningful clinical** benefit in:

1. Upright stability - ability to stand and walk
2. Bulbar function (speech and swallowing)

Measured in 146 adults and children at 72 weeks

Next steps:

PTC discussed with EMA if data could be used to apply for approval - expect to hear in 2024
Feb 2024 – Following meeting with FDA, PTC plan to submit new drug application in the US late 2024.
PTC exploring the need for additional trial based on FDA and EMA feedback

Opportunities to take part in research in the UK

27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

Natural history and progression studies

EFACTS natural history study - A study gathering information on the progression of FA over time

Balance and gait study - Uses wearable technology to investigate the impacts of FA on balance and gait, in the lab and in real-world settings

FA Global Clinical Consortium

- New consortium – 33 clinical sites, 18 countries
- The UNIFAI Study – harmonised study protocol
- Multi-site global natural history study
- EFACTS incorporated into this global study
- London Ataxia Centre (and other global sites)
- Data being used to design trials

FA studies – data provided by people with FA

FA Global Patient Registry

Many FA charities, including Ataxia UK, have patient registries to recruit for clinical trials and research studies. The FA Global Patient Registry (FAGPR) is a global effort to pool information in one place making it a more powerful resource for research.

Visit www.fapatientregistry.org/

The FA app

The charity End-FA set up an App for people with FA to facilitate research. Their aims are:

-Connect people with FA with researchers running clinical and virtual research trials

-Empower people with FA with useful tools for managing their life and treatment

-Educate people about symptoms, diagnosis and treatments, sharing the latest FA news

27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

www.thefaapp.org or download from **Apple store or Googleplay**

Healthcare or service improvement studies

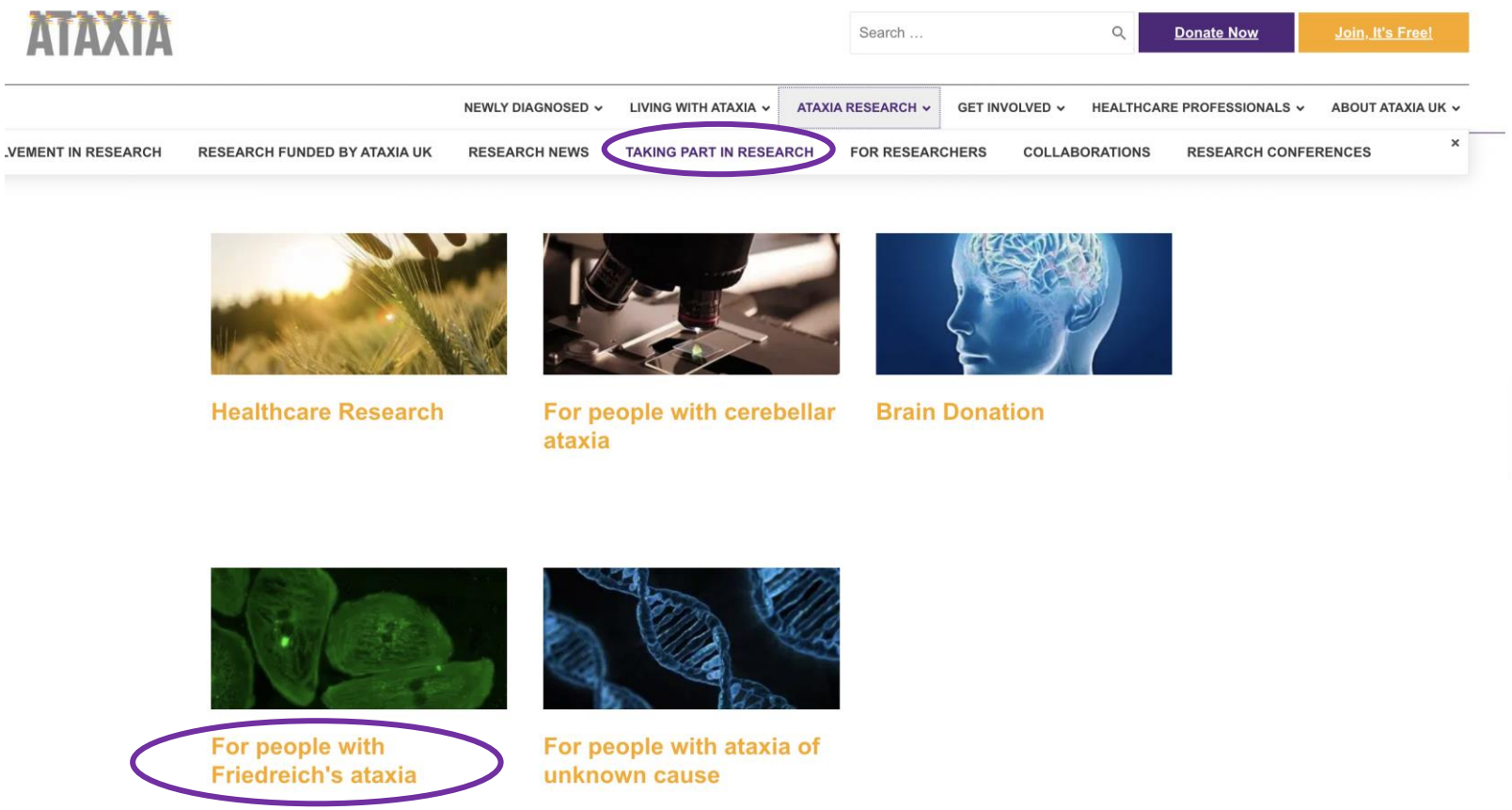
Project Euphonia

Aims to record speech samples to improve voice recognition software for people with dysarthria (speech that is difficult to understand).This is part of Google's AI for social good programme

LSVT Artic

Studies the impact of one-to-one speech therapy sessions, which are delivered online.

All studies can be found on our website ataxia.org.uk



27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

Thank you for listening!

27th & 28th September 2024

VIRTUAL ANNUAL CONFERENCE

www.ataxia.org.uk

Please contact research@ataxia.org.uk if you have any further questions!