Health Technology Briefing
August 2023

Omaveloxolone for the treatment of Friedreich's ataxia

Company/Developer	Reata Pharmaceuticals Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 10491	NICE TSID: N/A	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical trial.

Summary

Omaveloxolone is in development for the treatment of patients with Friedreich's Ataxia (FA). FA is an inherited disease that causes a range of symptoms including difficulty walking, inability to coordinate movements, muscle weakness, speech problems, damage to the heart muscle and diabetes. Patients with FA do not have enough frataxin, a protein that regulates iron in mitochondria (the energy-producing components of cells). As a result, iron builds up within the cells, which in turn results in the production of toxic forms of oxygen that damage cells in the brain, the spinal cord, and nerves, as well as in the heart and pancreas.

Omaveloxolone is an investigational oral drug that works by activating a protein called the nuclear factor erythroid 2-related factor 2 (Nrf2), which protects cells against toxic forms of oxygen. Omaveloxolone also blocks another protein called the nuclear factor-κB (NF-KB), which plays an important role in the inflammatory process. Through these actions, omaveloxolone is expected to protect cells and reduce inflammation, thus reducing the symptoms of FA. If licensed, omaveloxolone would provide a new treatment option for patients with FA.

Proposed Indication

Treatment of Friedreich's ataxia (FA) in adults and adolescents aged 16 to 40 years.[1]

Technology

Description

Omaveloxolone (RTA 408) is an investigational, oral, once-daily activator of nuclear factor-like 2 (Nrf2), a transcription factor that induces molecular pathways that promote the resolution of inflammation by restoring mitochondrial function, reducing oxidative stress, and inhibiting pro-inflammatory signalling.[2] A pre-clinical study that evaluated *in vitro* treatment with omaveloxolone showed the restoration of mitochondrial function in fibroblasts from FA patients and in neurons from multiple FA mouse models.[3,4]

Omaveloxolone is currently in development for the treatment of patients aged 16 years and above with FA. In the phase II clinical trial (NCT02255435; MOXIe), participants received an oral dose of omaveloxolone; between 2.5mg and 300mg daily for 10 to 48 weeks (please see trial record for full list of dosages).[1]

Key Innovation

On average, patients with FA die in their mid-thirties.[2] In most patients, symptoms begin between 5 and 15 years of age, and patients lose the ability to ambulate by their mid-20s. FA shortens life span, most often through consequences of cardiomyopathy; the mean age at death is 37.5 years. Effective treatment for FA remains challenging in the UK, as there are currently no approved therapies for FA, and more than 15 clinical trials have failed to reach their primary endpoints in recent years.[4]

Omaveloxolone may provide a new treatment pathway for patients with FA. In the Part 1 MOXIe trial, which evaluated omaveloxolone in the treatment of FA, omaveloxolone showed a significant neurological function improvement compared with a placebo and was generally safe and well tolerated.[4] If licensed, omaveloxolone may offer a new treatment option for patients with FA.

Regulatory & Development Status

Omaveloxolone does not currently have Marketing Authorisation in the EU/UK for any indication.

Omaveloxolone has been awarded the following regulatory designations:

- Orphan drug designation in the European Union (EU) in 2018 for the treatment of FA.[5]
- Orphan drug designation by the US Food and Drug Administration (FDA) for the treatment of FA.[2,6]
- Fast Track designation by the US FDA in November 2021 for the treatment of FA.[2,6]
- Rare Paediatric Disease Designation by the US FDA in May 2022 for the treatment of FA.[2,6]
- Priority Review Designation by the US FDA for the treatment of FA.[2,6]

Omaveloxolone is also in phase II/III development for the treatment of the following indications:[7]

- Breast cancer
- Melanoma
- Corneal endothelial cell loss
- Ocular inflammation and pain
- Mitochondrial myopathies

Patient Group

Disease Area and Clinical Need

FA is an inherited disease that causes a range of symptoms that worsen over time including difficulty walking, inability to coordinate movements, muscle weakness, speech problems, damage to the heart muscle and diabetes. Patients with FA do not have enough frataxin, a protein that regulates iron in mitochondria (energy-producing components of cells). As a result, iron builds up within the cells, which in turn results in the production of toxic forms of oxygen that damage cells in the brain, the spinal cord and nerves, as well as in the heart and pancreas.[5] FA is caused by an autosomal recessive inheritance of a defective frataxin gene (responsible for producing the frataxin protein), resulting in impaired frataxin protein production, which leads to the symptoms of FA.[8]

In 2021, it was estimated that FA affected approximately 0.5 in 10,000 people in the European Union (EU).[5,9] The incidence of FA in the UK is believed to be approximately 1 in every 50,000 and the prevalence 1 in 54,000.[9,10] In England (2021-22), there were 990 finished consultant episodes (FCEs) and 748 admissions for hereditary ataxia (ICD-10 code G11). This resulted in 375 day cases and 3,517 FCE bed days.[11] FA is the most common type of hereditary ataxia.[10]

Recommended Treatment Options

There are no National Institute for Health and Care Excellence (NICE) recommended treatments for FA.[12] Current strategies for the management of patients with FA centres on the treatment of FA symptoms, such as speech and language therapy, physiotherapy, occupational therapy, and other problems of the eye, bladder and muscle.[8,13]

Clinical Trial Information

Trial	**MOXIe**, NCT02255435, EudraCT 2015-002762-23; A Phase 2 Study of the Safety, Efficacy, and Pharmacodynamics of RTA 408 in the Treatment of Friedreich's Ataxia **Phase II** - Active, not recruiting **Location(s):** Two EU countries, UK, US, and Australia **Primary completion date:** October 2019
Trial Design	Randomised, parallel assignment, double masking and placebo-controlled
Population	N = 172 (actual); patients aged between 16 to 40 years with genetically confirmed Friedreich's ataxia
Intervention(s)	Omaveloxolone (RTA 408) Capsules administered orally. Part 1: dose-ranging study (2.5, 5, 10, 20, 40, 80, 160 and 300 mg) Part 2: Non-inferiority study over 48 weeks (150mg)
Comparator(s)	Matched placebo capsules administered orally.
Outcome(s)	Primary outcome measures: - Change From Baseline in Peak Work During Exercise Testing at Week 12 in Part 1 [Time Frame: Baseline through 12 weeks after participant receives the first dose in Part 1]. - Change in the Modified Friedreich's Ataxia Rating Scale (mFARS) at Week 48 in Part 2 [Time Frame: 48 weeks after participant receives the first dose in Part 2].

	See trial record for a full list of other outcomes
Results (efficacy)	Treatment with omaveloxolone met its primary endpoint or efficacy goal. At 48 weeks, patients taking omaveloxolone experienced statistically significant relief in muscular and neurological symptoms, corresponding to a 2.4-point reduction in mFARS scores compared to placebo.[14]
Results (safety)	Omaveloxolone was found to be generally well-tolerated and safe, with mild to moderate adverse events.[14]

Estimated Cost

The cost of omaveloxolone is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Corben, L.A., Collins, V., Milne, S. *et al.* Clinical management guidelines for Friedreich ataxia: best practice in rare diseases. 2022.[15]
- de Silva, R., Greenfield, J., Cook, A. *et al.* Guidelines on the diagnosis and management of the progressive ataxias. 2019.[16]
- Corben LA, Lynch D, Pandolfo M, Schulz JB, Delatycki MB; Clinical Management Guidelines Writing Group. Consensus clinical management guidelines for Friedreich ataxia. 2014.[17]

Additional Information

Reata Pharmaceuticals Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision-making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 ClinicalTrials.gov. *RTA 408 Capsules in Patients With Friedreich's Ataxia - MOXIe*. *Trial ID: NCT02255435*. 2014. Status: Active, not recruiting. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02255435 [Accessed 20 August, 2023].

2 Reata Pharmaceuticals. *Reata Pharmaceuticals Announces FDA Filing Acceptance and Priority Review Designation for the NDA for Omaveloxolone for the Treatment of Patients with Friedreich's Ataxia*. 2022. Available from: https://www.reatapharma.com/investors/news/news-details/2022/Reata-Pharmaceuticals-Announces-FDA-Filing-Acceptance-and-Priority-Review-Designation-for-the-NDA-for-Omaveloxolone-for-the-Treatment-of-Patients-with-Friedreichs-Ataxia/#:~:text=Omaveloxolone%20received%20Fast%20Track%20Designation%20in%20November%202021,treatment%2C%20diagnosis%2C%20or%20prevention%20of%20a%20serious%20condition [Accessed 28 July, 2023].

3 Abeti R, Baccaro A, Esteras N, Giunti P. Novel Nrf2-Inducer Prevents Mitochondrial Defects and Oxidative Stress in Friedreich's Ataxia Models. *Frontiers in Cellular Neuroscience*. 2018;12:188. Available from: https://doi.org/10.3389/fncel.2018.00188.

4 Lynch DR, Chin MP, Delatycki MB, Subramony SH, Corti M, Hoyle JC, et al. Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study). *Annals of Neurology*. 2021;89(2):212-25. Available from: https://doi.org/10.1002/ana.25934.

5 European Medicines Agency (EMA). *EU/3/18/2037: Orphan designation for the treatment of Friedreich's ataxia*. 2018. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-18-2037#:~:text=On%2027%20June%202018%2C%20orphan,%26%20Services%2C%20in%20November%202019. [Accessed 10 July 2023].

6 U.S. Food and Drug Administration (FDA). *FDA approves first treatment for Friedreich's ataxia*. 2023. Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-friedreichs-ataxia [Accessed 28 July, 2023].

7 ClinicalTrials.gov. *Omaveloxolone | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Phase 2, 3*. 2023. Available from: https://classic.clinicaltrials.gov/ct2/results?term=Omaveloxolone&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 28 July, 2023].

8 Ataxia UK. *Friedreich's ataxia: the facts*. 2023. Available from: https://www.ataxia.org.uk/wp-content/uploads/2020/11/Friedreichs_ataxia_booklet_2015fd15.pdf [Accessed 19 July 2023].

9 Vankan P. Prevalence gradients of Friedreich's Ataxia and R1b haplotype in Europe co-localize, suggesting a common Palaeolithic origin in the Franco-Cantabrian ice age refuge. *Journal of Neurochemistry*. 2013;126(s1):11-20. Available from: https://doi.org/10.1111/jnc.12215.

10 National Health Service (NHS). *Ataxia Types: Friedreich's ataxia*. 2021. Available from: https://www.nhs.uk/conditions/ataxia/symptoms/ [Accessed 20 July 2023].

11 National Health Service (NHS) 75 Digital. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 19 April 2023].

12 National Institute for Health and Care Excellence (NICE). *Friedreich's ataxia*. 2023. Available from: https://www.nice.org.uk/search?q=Friedreich%27s+ataxia [Accessed 20 July 2023].

13 National Health Service (NHS). *Ataxia treatment*. 2021. Available from: https://www.nhs.uk/conditions/ataxia/treatment/ [Accessed 20 July 2023].

14 Friedreich's Ataxia News. *MOXIe Trial of Omaveloxolone Shows Significant Benefit to FA Patients, Reata Reports*. 2019. Available from: https://friedreichsataxianews.com/news/topline-results-moxie-trial-omaveloxolone-show-significant-benefits-fa-reata-reports/?cn-reloaded=1 [Accessed 10 July 2023].

15 Corben LA, Collins V, Milne S, Farmer J, Musheno A, Lynch D, et al. Clinical management guidelines for Friedreich ataxia: best practice in rare diseases. *Orphanet Journal of Rare Diseases*. 2022;17(1):415. Available from: https://doi.org/10.1186/s13023-022-02568-3.

16 de Silva R, Greenfield J, Cook A, Bonney H, Vallortigara J, Hunt B, et al. Guidelines on the diagnosis and management of the progressive ataxias. *Orphanet Journal of Rare Diseases*. 2019;14(1):51. Available from: https://doi.org/10.1186/s13023-019-1013-9.

17 Corben LA, Lynch D, Pandolfo M, Schulz JB, Delatycki MB. Consensus clinical management guidelines for Friedreich ataxia. *Orphanet Journal of Rare Diseases*. 2014;9:184. Available from: https://doi.org/10.1186/s13023-014-0184-7.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.