

SKYCLARYS®

Category:

Best Product for Orphan/Rare Diseases

Company Name:

Biogen

Product/Solution Name:

SKYCLARYS® (omaveloxolone)

Compound/Tech Name:

Omaveloxolone

Trade Name:

SKYCLARYS®

Corporate Name:

SKYCLARYS®

Date of Approval:

2023-02-28

Indications:

SKYCLARYS is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

Therapeutic Areas:

Friedreich's ataxia

General Information File Document upload:

[Prix Galien_SKYCLARYS_Final.pdf](#)

Background information and need for drug / device:

Friedreich ataxia (FA) is a rare, genetic, debilitating, and degenerative neuromuscular disorder estimated to impact more than 5,000 people in the United States and 22,000 individuals globally. Despite its relative rarity in the population, it is the most commonly inherited ataxia. FA is primarily caused by a mutation in the frataxin gene, leading to the deficiency in normal frataxin protein levels and a subsequent dysfunction in mitochondria. Without normal levels of frataxin, certain organs in the body, especially peripheral nerve, spinal cord, brain, heart, muscle, and pancreas may not function properly. This leads to various symptoms, including awkward, unsteady movements and impaired muscle coordination that worsens over time, difficulty walking and poor balance, impaired sensory functions, such as loss of sensation in the arms and legs which may spread to the trunk and other parts of the body, loss of normal reflexes, slurred speech, spasticity, difficulty swallowing, hearing loss, vision loss, fatigue, heart disease, and diabetes. Early symptoms of FA typically appear in childhood with most people living with FA needing a wheelchair within 10-20 years of their first symptoms.

As the patient's ataxia progresses, the symptoms of the disorder become worse; speech will become progressively impaired leading to communication breakdown and feelings of isolation. Eventually, even the patient's swallowing function deteriorates, leading to pneumonias and the need for tube feeding and ultimately, to hospitalization and death. The reported average age of death for people with FA is just 37 years old, largely due to heart disease associated with FA. Approved in 2023, SKYCLARYS is the first treatment for FA.

Background File Document upload:

N/A

History of the development of the solution/product:

The benefit and risk profile of omaveloxolone was evaluated in the 3-part clinical trial, MOXle, that assessed patients with Friedreich's ataxia (FA). MOXle Part 1 was a randomized, placebo-controlled, 12-week, dose ranging study of total 69 patients and looked for an optimal dose using pharmacodynamic markers and the modified Friedreich ataxia rating scale (mFARS). MOXle Part 2 was a randomized, placebo-controlled, 48-week study of 103 total patients, designed to assess for a treatment effect on mFARS. Omaveloxolone met primary endpoint of the pivotal study in the FA population. The results of the Moxie part 2 study were numerically internally consistent, and improvements with omaveloxolone were concordant across multiple clinical measures that impact the quality of life for patients with FA. The Moxie part 2 data was key for the approval of the New Drug Application through the FDA. We have included graphs below visually representing the results from the part 2 portion of the MOXle trial.

Finally, the third part of MOXle, the open-label extension (MOXle Extension), led to two additional exploratory post hoc analyses of long-term treatment that supported long-term efficacy of omaveloxolone. The first additional analysis was delayed-start analysis. The second analysis, the propensity matched analysis, was designed to evaluate the long-term efficacy of omaveloxolone in pooled population in MOXIE extension comparing to matched patients from an external natural history cohort from FA-COMS. This data suggested longer term treatment benefit, with evidence of 55% slowing of disease progression compared to a propensity score matched natural history population (as assessed by mFARS) after 3 years of follow-up. As this was an exploratory analysis, conclusions cannot be drawn.

The collective data and consistency of findings from the single positive study accompanied by evidence of long-term treatment benefit provided substantial evidence of effectiveness of omaveloxolone in the treatment of patients with FA. In addition, omaveloxolone was generally well tolerated. Given the serious and life-threatening nature of FA and the substantial unmet medical needs with no approved treatment, omaveloxolone received orphan drug designation and obtained FDA approval in February 2023 and EMA approval in February 2024 for the treatment of patients with FA aged 16 years and older.

Development File Document upload:

N/A

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

SKYCLARYS is the first and only FDA-approved treatment for Friedrich ataxia, currently indicated for patients 16 years and older. Pre-launch market research found that roughly half of people diagnosed with FA had not seen a neurologist in the previous five years, indicating that the absence of a treatment had disconnected patients from care. Now, for the first time, the people living with FA have the chance to change the course of their lives with SKYCLARYS. Moreover, health care professionals have an innovation designed specifically to address the progression of FA that is transforming management of FA.

The approval of SKYCLARYS blazed a new path for supportive evidence by using a propensity matched comparison to an external control group, an unprecedented approach. This is a significant innovation especially for drug development in rare diseases where there are often meaningful recruitment challenges. This approach to generating evidence was made possible by work started over 20 years ago by the Friedreich's Ataxia Research Alliance (FARA) to establish a natural history study, define an endpoint to track progression, and identify factors prognostic for disease

progression. This work was leveraged along with the substantial natural history data to calculate propensity scores that would enable selection of a matched control group from the natural history data for comparison with the open-label extension data.

Leveraging the natural history comparison for supportive evidence resulted in a robust data package. The supportive evidence of long-term treatment benefit compared to a propensity matched natural history helped reinforce the results of the 1-year placebo-controlled pivotal study. It also provided additional information about the durability of the treatment effect through the 3-year propensity matched analysis.

These data supported the approval of SKYCLARYS by the FDA in February 2023, which gave patients living with FA the first ever treatment option, and most importantly, hope. Now 1-year post-launch, over 1,100 patients are on treatment in the U.S. alone, with at least 15 other markets planning to make SYCLARYS available in 2024.

Innovation File Document upload:

N/A

Please provide appropriate references (PubMed, Abstract, Website):

1. Friedreich's Ataxia Research Alliance. "What is FA?" Available at: <https://www.curefa.org/what-is-friedreichs-ataxia#>.
2. National Institute of Neurological Disorders and Stroke. Friedreich Ataxia. Available at: <https://www.ninds.nih.gov/health-information/disorders/friedreich-ataxia>. Accessed February 2024.
3. Schulz JB, Boesch S, Bürk K, Dürr A, Giunti P, Mariotti C, Pousset F, Schöls L, Vankan P, Pandolfo M. Diagnosis and treatment of Friedreich ataxia: a European perspective. *Nat Rev Neurol*. 2009 Apr;5(4):222-34. doi: 10.1038/nrneurol.2009.26. PMID: 19347027.
4. Fogel BL, Perlman S. Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. *Lancet Neurol*. 2007 Mar;6(3):245-57. doi: 10.1016/S1474-4422(07)70054-6. PMID: 17303531.
5. Lynch DR, Goldsberry A, Rummey C, Farmer J, Boesch S, Delatycki MB, Giunti P, Hoyle JC, Mariotti C, Mathews KD, Nachbauer W, Perlman S, Subramony SH, Wilmot G, Zesiewicz T, Weissfeld L, Meyer C. Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data. *Ann Clin Transl Neurol*. 2024 Jan;11(1):4-16. doi: 10.1002/acn3.51897. Epub 2023 Sep 10. PMID: 37691319; PMCID: PMC10791025.
6. Lynch DR, Chin MP, Delatycki MB, Subramony SH, Corti M, Hoyle JC, Boesch S, Nachbauer W, Mariotti C, Mathews KD, Giunti P, Wilmot G, Zesiewicz T, Perlman S, Goldsberry A, O'Grady M, Meyer CJ. Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study). *Ann Neurol*. 2021 Feb;89(2):212-225. doi: 10.1002/ana.25934.

Epub 2020 Nov 5. Erratum in: Ann Neurol. 2023 Dec;94(6):1190. PMID: 33068037; PMCID: PMC7894504.

7. Bürk K. Friedreich Ataxia: current status and future prospects. Cerebellum Ataxias. 2017 Apr 7;4:4. doi: 10.1186/s40673-017-0062-x. PMID: 28405347; PMCID: PMC5383992.

References File Document upload:

N/A