New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Skyclarys™ (omaveloxolone) [Reata Pharmaceuticals]** (skye klar' is)
Dosage Formulations:	Capsules: 50 mg
FDA Approval Date: **FDB File Date:**	FDA: February 28, 2023 FDB: March 19, 2023
Indication:	Treatment of Friedreich's ataxia (FA) in adults and adolescents ≥ 16 years of age.
Mechanism of Action:	The precise mechanism by which Skyclarys exerts its therapeutic effect in patients with Friedreich's ataxia is unknown. Skyclarys has been shown to activate the nuclear factor (erythroid-derived)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress.
Dose/ Administration:	• The recommended dosage of Skyclarys is 150 mg (3 capsules) taken orally once daily. • Administer Skyclarys on an empty stomach at least one hour before eating • Swallow Skyclarys capsules whole. Do not open, crush, or chew.
Disease State Clinical Highlights:	• FA is a rare, progressive, autosomal recessive genetic neurodegenerative disorder and is one of the most common hereditary ataxias. It primarily affects the function of the cerebellum, spinal cord, and peripheral nervous system. FA can also cause diabetes mellitus, cardiomyopathy, scoliosis, and pes cavus. Pes cavus is a type of foot deformity, where the arch becomes abnormally high due to selective denervation of the leg muscles. Pes cavus tends to worsen with the progression of the neurodegeneration seen in FA and occurs in about half of the people diagnosed with FA. • The onset of FA is usually between the ages of 10 to 15 years but has been diagnosed in people from the ages of 2 to 50. FA typically is diagnosed before the age of 25. Late-onset FA is characterized by symptom onset after the age of 25 and is found in about 14% of patients diagnosed with FA. In very late-onset FA, symptoms present after the age of 40, however this diagnosis is very rare. Average time from onset to requiring a wheelchair is about 10 to 20 years. More than 95% of patients with FA will become wheelchair bound by 45 years of age. The average lifespan of a patient with FA is about 40 years, with the main cause of death being cardiac dysfunction. • FA is diagnosed though genetic testing. In about 98% of people with FA, the most common cause of the disease is a homozygous guanine–adenine–adenine triplet repeat expansion (GAA) in the frataxin (FXN) gene. These patients have more than 120 repeats of the GAA sequence. The more repeats the patient has, the more likely they are to have disease onset at a young age, more severe symptoms, more rapid disease progression and an earlier death. For every 100 GAA repeats, there is an earlier disease onset of 2.3 years. Less than 300 repeats is linked to later disease onset, less severe symptoms, and a better prognosis. In the other 2% of patients diagnosed with FA, the disease is due to compound heterozygosity for a GAA expansion and a point mutation or deletion with Gly130Val being the most common point mutation. These patients usually have a later age of onset and slower disease progression, and do not have dysarthria or cardiomyopathy. • Because decreased FXN protein is produced, disease results in iron accumulation, mitochondrial dysfunction, and oxidative damage. This causes the neurological symptoms, diabetes mellitus, cardiomyopathy and musculoskeletal deformities associated with FA. • The overall prevalence of FA is approximately 1 in 40,000 to 50,000 people. An estimated 4,000–5,000 individuals in the United States and about 15,000 to 22,000 worldwide have FA.

- There is no cure for FA and there are currently no other pharmacological agents to treat, modify, delay, or prevent the disease. Treatment is supportive and symptomatic in nature.

Drug Clinical Highlights:

- Skyclarys is the first treatment available for Friedreich's ataxia in the United States.
- Skyclarys received fast track designation and a rare pediatric disease designation from the FDA.
- Skyclarys will only be available through the specialty pharmacy, Biologics by McKesson.
- Contraindications: none
- Adverse Drug Reactions (ADRs): The most common adverse reactions (incidence ≥ 20% and greater than placebo) were increased alanine aminotransferase (ALT), increased aspartate aminotransferase, (AST), headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain.
- Warnings and Precautions:
  - Elevation of Aminotransferases: Monitor ALT, AST, and total bilirubin prior to initiation, every month for the first 3 months of treatment, and periodically thereafter.
  - Elevation of B-type Natriuretic Peptide (BNP): Advise patients of signs and symptoms of fluid overload.
  - Lipid Abnormalities: Monitor cholesterol periodically during treatment.
- Drug Interactions:
  - Recommended Dosage with Concomitant Use of CYP3A4 Inhibitors and Inducers:

Concomitant Drug Class	Dosage
Strong or Moderate CYP3A4 Inducer	Avoid concomitant use.
Strong CYP3A4 Inhibitor	Avoid concomitant use if coadministration is avoidable. If coadministration is unavoidable: • Reduce Skyclarys dose to 50 mg once daily with close monitoring for ADRs • If ADRs emerge, the strong CYP3A4 inhibitor should be discontinued.
Moderate CYP3A4 Inhibitor	Avoid concomitant use. If coadministration is unavoidable: • Reduce Skyclarys dose to 100 mg once daily with close monitoring for ADRs. • If ADRs emerge, reduce Skyclarys dose to 50 mg once daily.

  - Recommended Dosage in Patients with Hepatic Impairment:

Hepatic Impairment Classification (Child-Pugh)	Dosage
Mild (Child-Pugh Class A)	150 mg once daily
Moderate (Child-Pugh Class B)	• 100 mg once daily with close monitoring for ADRs. • Reduce to 50 mg once daily if ADRs are present.
Severe (Child-Pugh Class C)	Avoid use

  - Concomitant use with Skyclarys can reduce the exposure of CYP3A4 and CYP2C8 substrates which may reduce the activity of these substrates. Refer to the prescribing information of substrates of CYP3A4 and CYP2C8 for dosing instructions if used concomitantly with Skyclarys and monitor for lack of efficacy of the concomitant treatment.

- Concomitant use of hormonal contraceptives with Skyclarys may reduce the efficacy of hormonal contraceptives. Counsel females using hormonal contraceptives to use an alternative contraceptive method (e.g., non-hormonal intrauterine system) or additional non-hormonal contraceptive (e.g., condoms) during concomitant use and for 28 days after discontinuation of Skyclarys.
- Avoid grapefruit juice and grapefruit while taking Skyclarys.

- Use in Specific Populations:
  - Pregnancy: Based on animal data, may cause fetal harm.
  - Lactation Risk: There are no data on the presence of Skyclarys or its metabolites in human milk. The effects on milk production and the breastfed infant are unknown. Skyclarys was excreted in the milk of lactating rats following oral administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Skyclarys and any potential adverse effects on the breastfed infant from Skyclarys or from the underlying maternal condition.
- The magnitude of improvement seen with Skyclarys is equivalent to approximately 2 years of disease progression in patients with FA; therefore, Skyclarys may delay the progression of FA.

Skyclarys Clinical Trials

- MOXIe Part 1 Clinical Study
  - 12-week, international, multicenter, randomized, double-blind, placebo-controlled, dose-ranging trial in 69 patients with FA.
  - Part 1 of MOXIe was designed to identify a safe and clinically active dose of Skyclarys to study in Part 2.
  - The 160 mg dose provided the maximum effect on the primary endpoint of change in mFARS score (see below).
  - 150 mg was chosen as the starting dose for MOXIe Part 2 to decrease the pill burden associated with the 160 mg dosing.
- MOXIe Part 2 Study

Study Design	• Phase 2, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, registrational trial
Inclusion Criteria	• Males and females between 16 and 40 years of age • Genetically confirmed FA • Baseline mFARS scores between 20 and 80 (see below) • Able to complete maximal exercise testing on a recumbent stationary bicycle
Exclusion criteria	• Uncontrolled diabetes (HbA1c > 11% • BNP > 200 pg/mL • Clinically significant left-sided heart disease or clinically significant cardiac disease • Active infection • Significant laboratory abnormalities or interfering medical conditions • Non-ambulatory patients
Intervention	Skyclarys 150 mg once daily (n=51) or placebo (n=52) for 48 weeks

Primary Endpoint	• Mean change in mFARS (modified Friedreich's Ataxia Rating Scale) score from baseline to Week 48
	  ○ The mFARS is a physician-assessed neurologic exam that tracks progression of FA. The scale consists of four sections and scores range from 0 to 93. Lower scores indicate better neurologic function
	  ○ Patients with FA typically progress an average of 1 to 2 points per year on mFARS over time and do not improve

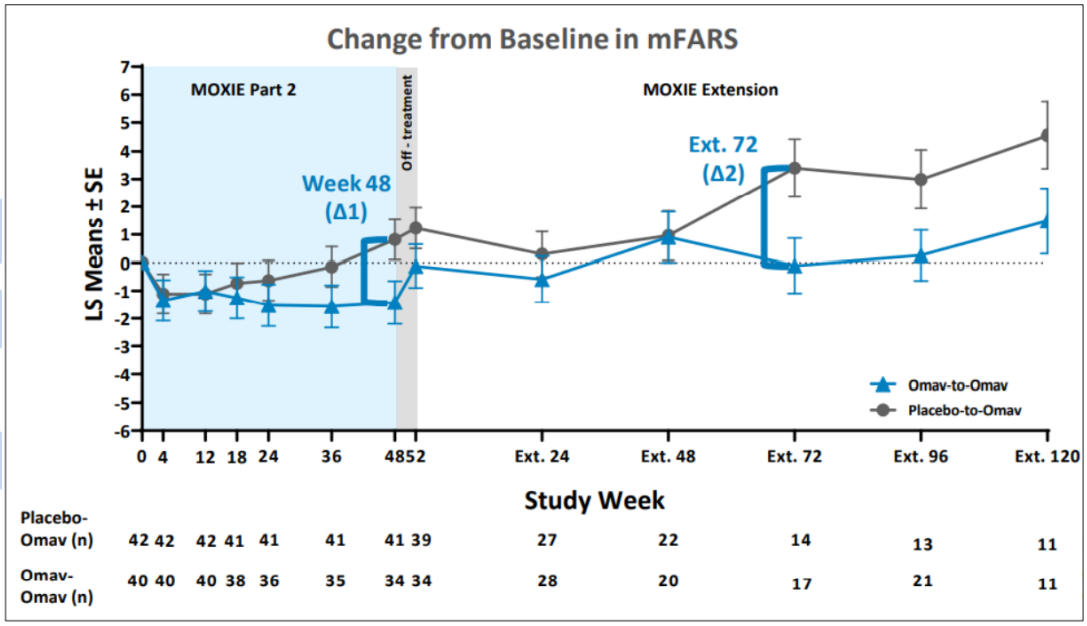
Secondary Endpoints	• Mean change in patient global impression of change (PGIC) score from baseline to Week 48
	  ○ The patient ranks their change following an intervention on a scale from 1 to 7, with 1 representing "no change" and 7 representing "a great deal better".
	• Mean change in Clinical Global Impression of Change (CGIC) from baseline to Week 48
	  ○ Clinicians rank patients' change following an intervention on a scale from 1 to 7. A score of 1 represents "very much improved" and a score of 7 represents "very much worse."
	• Mean change in 9 Hole Peg Test (9-HPT) from baseline to Week 48
	  ○ A brief, standardized, quantitative test of upper extremity function.
	• Mean change in a Timed 25 Minute Foot Walk (T25-FW).
	  ○ This test is based on the reciprocal of average walk time from baseline to Week 48.
	  ○ Quantitative mobility and leg function performance test
	• Mean change in median frequency of falls (min, max) from baseline to Week 48
	• Mean change in peak workload (watts/kg) in maximal exercise testing from baseline to Week 48.
	• Mean change in Friedreich's ataxia activities of daily living (FA-ADL)
	  ○ Scored from 0 to 36, with higher scores representing more severe progression

- Primary Endpoint Results (mFARS change from baseline at week 48)

	Skyclarys (n=40)	Placebo (n=42)
mFARS baseline score	40.9	38.8
Week 48 Change from Baseline, mean	-1.55 +/- 0.69 points (95% CI: -2.93 to -0.18)	0.85 +/- 0.64 points (95% CI: -0.43 to 2.13)
Mean difference between treatment groups	-2.40 +/- 0.96 points (95% CI: -4.31 to -0.5) (P= 0.014)	

- Secondary Endpoint Results:
  - The study was not powered to detect a statistical difference between treatment groups in the secondary endpoints.
  - Skyclarys did not significantly improve any secondary efficacy measures relative to placebo.
  - Some measures are not expected to change within 1 year based on natural history data in patients with FA.
- Patients with pes cavus experienced the least improvements in mFARS scores.
- MOXIe Extension Study

- The Extension phase of the trial assessed the long-term safety and tolerability of Skyclarys in qualified patients with FA following completion of Part 1 or Part 2. There were a total of 149 patients enrolled (57 patients from MOXIe Part 1 and 92 patients from MOXIe Part 2).
- This study was completed in December 2022.
- This analysis compared the change from baseline in mFARS for patients without pes cavus randomized to placebo during MOXIe Part 2 (placebo to Omav) to patients randomized to Skyclarys during MOXIe Part 2 (Omav to Omav).
- If the treatment effect at MOXIe Extension Week 72 is maintained or noninferior to the treatment effect at MOXIe Part 2 Week 48, it demonstrates evidence of a persistent effect on the disease course. If the treatment effect is not maintained and the patients originally randomized to placebo are able to achieve the same absolute response and "catch up" to the patients initially randomized to Skyclarys, the results are consistent with a symptomatic treatment that does not affect the underlying course of the disease.
- More than 50% of the difference between groups in mFARS observed at MOXIe Part 2 Week 48 (−2.25, P = 0.037) was preserved at MOXIe Extension Week 72 (−3.51, P = 0.016).
- In the MOXIe Extension phase, patients taking Skyclarys progressed at a rate of 0.5 points on the mFARS scale, while natural progression of the diseases increases at a of 2 points per year on the mFARS scale.
- Overall, the Delayed-Start analysis results indicate a persistent Skyclarys treatment effect on the course of FA. Figure 1 shows the Delayed-Start analysis change from baseline in mFARS.



- Populations that experienced the greatest improvements in mFARS:
  - Patients <18 years of age
  - Males
  - GAA repeat length ≥675
- Safety
  - Serious adverse drug reactions occurred in five Skyclarys-treated patients (10%) and three placebo-treated patients (6%).
  - Discontinuations due to adverse events occurred in 8% of the Skyclarys-treated group and in 4% of the placebo treated group.
  - Skyclarys-treated patients also experienced mean decreases in weight relative to baseline and to placebo-treated patients at Week 48; this was seen in adult patients and was more pronounced in overweight patients.

	○ Skyclarys did not increase blood pressure and did not demonstrate adverse effects on ventricular heart rate, QT interval corrected by Fridericia's formula (QTcF), wall thickness, or ejection fraction.
Price Per Unit (WAC):	• The cost per 50 mg capsule is $342.59, which equals a daily price of $1,027.77. • Estimated annual price is $375,000 per year.
Therapeutic Alternatives:	• Skyclarys is the first medication that is FDA-approved to treat FA. • Over the counter products have been investigated to treat FA including vitamin E, coenzyme Q10 and idebenone (a synthetic analogue of coenzyme Q10). Vitamin E protects polyunsaturated fatty acids in membranes from attack by free radicals. Coenzyme Q10 and idebenone reduce free radicals, inhibits lipid peroxidation, and consequently protect the mitochondria from oxidative damage. Results for the International Cooperative Ataxia Rating Scale (ICARS) scores in patients with FA did not reveal any significant difference between the antioxidant-treated and the placebo groups.
Prior Authorization Approval Criteria:	**Must meet the following criteria:** Initial Therapy: • Participant is aged 16 years or older **AND** • Participant has a genetically confirmed diagnosis of FA (loss-of-function mutations in the FXN gene located on chromosome 9q13, with 66 to 1700 GAA repeats, ICD-10 code of G11.11) **AND** • Prescribed by or in consultation with a neurologist or other specialist in the treated disease state **AND** • Baseline mFARS score Continuation of Therapy: • Documentation of benefit of therapy defined by mFARS score less than or equal to baseline. Denial Criteria: • Therapy will be denied if all approval criteria are not met • Participant is currently pregnant. Default Approval Period: • 1 year **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Liver function tests should be performed prior to initiating Skyclarys, every month for the first 3 months of treatment, and periodically thereafter as needed. • BNP should be performed prior to initiating Skyclarys and if signs and symptoms of fluid overload occur, such as sudden weight gain, peripheral edema, palpitations, and shortness of breath. Advise patients to contact their healthcare provider if signs and symptoms of fluid overload develop. • Cholesterol should be assessed prior to starting Skyclarys and monitored periodically during treatment because it has been associated with increases in LDL cholesterol and decreases in HDL cholesterol. • Assess for potential drug-drug interactions with Skyclarys including other prescription medications, non-prescription medications, or herbal products. • Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during Skyclarys therapy.

- Counsel females using hormonal contraceptives to use an alternative contraceptive method (e.g., non-hormonal intrauterine system) or additional non-hormonal contraceptive (e.g., condoms) during concomitant use and for 28 days after discontinuation of Skyclarys.

Implication to State Medicaid Program:

LOE: 2/28/2037

- Other Indications for Skyclarys being explored in clinical trials
  - Mitochondrial Myopathy (MOTOR, NCT02255422)
  - Melanoma (REVEAL, NCT02259231 with expanded access in NCT03593499)
  - Lotion for radiation dermatitis (PRIMROSE, NCT02142959)
  - Ophthalmic Suspension for the Prevention of Corneal Endothelial Cell Loss Following Cataract Surgery (GUARD, NCT02128113)
  - Ophthalmic Suspension for the Treatment of Ocular Inflammation and Pain Following Ocular Surgery (NCT02065375)
- NRF2 Activators in Pipeline

Prescription and Pipeline Products	Class	Status	Comments
Resveratrol	NRF2 activator	Phase 2	• This study aims to determine the effect of two doses of resveratrol (1 g/day and 5 g/day) taken for 12 weeks on frataxin levels in individuals with Friedreich ataxia • Additional outcome measures include the effect of resveratrol on markers of oxidative stress, clinical measures of ataxia, and cardiac parameters.
Dimethyl Fumarate (DMF)	NRF2 activator	None	• Not currently FDA-approved to treat FA. • No current clinical trials taking place for patients with FA. • DMF increases FXN expression in FA cell model, FA mouse model and in DMF-treated patients. • Patients with multiple sclerosis taking DMF showed significant increase (about 85%) in FXN expression.

- Other Medications to Treat FA in Pipeline

Prescription and Pipeline Products	Class	Status	Comments
Pioglitazone	PPAR gamma agonist	Phase 3	• Enhances mitochondrial function, reduces generation of reactive oxygen species (ROS) and enhances antioxidant defense.
MIN-102; leriglitazone	PPAR gamma agonist (Metabolite of pioglitazone)	Phase 2	• Modulates frataxin-controlled metabolic pathways. • Selective PPAR agonist which restores mitochondrial function and energy production • Suspension formulation
RT-001; deuterated linoleic acid	Synthetic homologue of linoleic acid	Phase 3	• Improves mitochondrial function and reduces oxidative stress. • Downregulates lipid peroxidation to protect cell and mitochondrial membranes from degeneration.

				• Granted Orphan Drug, Rare Pediatric Disease, and Fast Track designations for FA.
	PTC-743; vatiquinone	Para-benzoquinones	Phase 3	• Improves mitochondrial function and reduces oxidative stress. • Inhibits 15-lipoxygenase, a key enzyme that regulates inflammation and oxidative stress. • Granted Orphan Drug and Fast Track designations for FA. • Derivative of vitamin E.

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