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New Drug Evaluation: Omaveloxolone Oral Capsules

Date of Review: June 2023
Generic Name: Omaveloxolone

End Date of Literature Search: 03/09/23
Brand Name (Manufacturer): Skyclarys™ (Reata Pharmaceuticals, Inc.)

Dossier Received: yes

Plain Language Summary:

- This review looks at evidence for the safety and effectiveness of omaveloxolone oral capsules. Omaveloxolone is the first medicine approved in the United States to treat a condition known as Friedrich's ataxia.
- Friedreich's ataxia is a rare, inherited disease that causes damage to the nervous system and decreases the length of life of people with this condition. People with Friedreich's ataxia usually start to have symptoms in childhood or as young adults. People with Friedreich's ataxia have unsteady balance, muscle weakness and it becomes harder to walk, dress, and speak as time goes on. The main goals of therapy are to treat the symptoms and provide support. Until recently, there were no medicines approved to treat this condition.
- Omaveloxolone improved coordination in people with Friedrich's ataxia in a single 48-week study.
- Omaveloxolone may increase liver function tests. These changes in test results were temporary and returned to normal when omaveloxolone was discontinued. Other side effects seen from people in the study were nausea, headache, stomach pain, diarrhea, and feeling tired.
- Providers who prescribe omaveloxolone to a person enrolled in the Oregon Health Plan must explain to the Oregon Health Authority why someone needs omaveloxolone before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

- What is the evidence for the efficacy of omaveloxolone for treatment of Friedrich's ataxia in adults and adolescents?
- What are the harms associated with the use of omaveloxolone?
- Are there specific populations or communities, based on demographic characteristics, who would be more likely to benefit or be harmed from the use of omaveloxolone?

Conclusions:

- Omaveloxolone is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.[1] Omaveloxolone oral capsules received Food and Drug Administration (FDA) approval in February 2023 with priority review under orphan drug status and rare pediatric disease designation.[2] The efficacy and safety of omaveloxolone to treat Friedreich's ataxia were evaluated in a multi-center, placebo-controlled, double-blind, Phase 2 randomized trial (MOXIe).[2,3]

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- In the MOXIe study, 103 patients were randomized 1:1 to omaveloxolone 150 mg once a day (n=51) or placebo (n=52) for 48 weeks to evaluate safety and efficacy of omaveloxolone.[2] The primary analysis was the change from baseline in the modified Friedreich's Ataxia Rating Scale (mFAR) score for people who received omaveloxolone compared to placebo after 48 weeks of treatment in the full analysis population of patients (n=82).[2] The minimum score for the mFARS is 0 and the maximum score is 93.[2] A lower score indicates better neurological function and less physical impairment.[2] Improvement was defined by the investigators was an increase of no more than 1.9 points in mFAR score from baseline.[2] At 48 weeks, low quality-evidence showed mean mFAR scores (scale 0-99) improved by 1.55 points in the omaveloxolone group and worsened by 0.85 points in the placebo group (mean difference between groups -2.4 points; 95% confidence interval [CI] -4.3 to -0.5; p=0.014).[2] The clinical significance of this difference for a 99-point scale is unclear.
- The most common adverse effects of omaveloxolone observed in clinical trials were transient increases in alanine transaminase (ALT) and aspartate aminotransferase (AST), headache, nausea, abdominal pain, fatigue, diarrhea and musculoskeletal pain.[1] In part 2 of the MOXIe trial, increases in BNP above the upper limit of normal (100 pg/mL) were observed in 14% of omaveloxolone-treated patients (compared with 4% of placebo-treated patients).[2] The manufacturer recommends obtaining ALT, AST, bilirubin, B-type natriuretic peptide (BNP), and lipid parameters prior to initiating treatment and periodically during treatment.[1]
- Omaveloxolone is contraindicated in patients with severe hepatic impairment. In patients with moderate hepatic impairment the omaveloxolone dose should be adjusted to 100 mg once daily.[1] Due its hepatic metabolism by CYP3A4 enzymes, there are numerous drug interactions between omaveloxolone and other medications. The omaveloxolone dose should be adjusted to 50 or 100 mg once daily when co-administered with strong or moderate CYP3A4 inhibitors, respectively.[1]
- Ninety-seven percent of study participants in the MOXIe study were white,[2] non-white populations were not represented in the study; this undermines confidence in this evidence applies communities served by OHP.

Recommendation:

- Maintain omaveloxolone as non-preferred on the Practitioner-Managed Prescription Drug Plan (PMPDP) with clinical prior authorization (PA) criteria to ensure medically appropriate use.

Background:

Friedreich's ataxia, is a rare, progressive, autosomal recessive, neurodegenerative disorder. It is the most common hereditary ataxia in people of Western European descent.[4] The estimated prevalence of Friedreich's ataxia in European populations is 1 in 50,000.[5] In the United States, prevalence is approximately 5,000 people.[2] The prevalence of this condition is lowest in China, Japan, and sub-Saharan Africa.[4] Within the Oregon Health Plan (OHP), 30 people enrolled during 2022 have Friedreich's ataxia, with most of these people receiving care in through a coordinated care organization (CCO).

Friedreich's ataxia is associated with mutations in the frataxin gene located on chromosome 9q13, which leads to impaired transcription of the protein, frataxin.[6] Patients with Friedrich's ataxia have expanded guanine-adenine-adenine (GAA) trinucleotide repeats of both alleles of the frataxin gene.[6] In Friedrich's ataxia, the number of GAA repeats can vary from 66 to 1700, compared with 7 to 34 in a normal allele.[5] The larger expansions of GAA repeats are associated with increased severity of this condition.[6] Frataxin is essential for normal mitochondrial function and adenosine triphosphate (ATP) production.[6] Frataxin deficiency is associated with abnormal accumulation of intramitochondrial iron, defective mitochondrial respiration, and overproduction of oxygen free radicals, causing cell damage.[2,4] Studies have also demonstrated that nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) signaling is impaired in patients with Friedreich's ataxia.[2] In healthy people, oxidative stress causes Nrf2 to increase the expression of antioxidant genes, which protect cells from damage.[2] The recently approved treatment for Friedrich's ataxia, omaveloxolone, is an activator of Nrf2 signaling.[2]

Friedreich's ataxia presents as impaired coordination of both arms and legs, loss of normal reflexes in the ankles and knees, vision and hearing loss, slurred speech, scoliosis, and increased spasticity.[5] The onset of symptoms is usually before 20 years of age, and the symptoms will continue to progress with increasing difficulty in balance, gait, and activities of daily living (i.e., writing, dressing, washing and feeding).[5] Age of onset is an important predictor of disease severity and the speed of disease progression.[7] Children diagnosed with early onset Friedreich ataxia before 7 years of age tend to have more genetic mutations and severe symptoms that rapidly progress to impaired neuromuscular abilities.[7] Skeletal deformities and cardiomyopathy are found in a majority of patients, who also have an increased frequency of impaired glucose tolerance and diabetes.[5] Most early-onset patients will be wheel-chair dependent by their late teens or early twenties.[5] The mean age of death is 37.5 years, although some patients with late-onset ataxia (after 25 years of age) have survived until they reached 80 years of age.[4] The major cause of death is congestive heart failure or cardiac arrhythmia.[8,9]

The diagnosis of Friedrich's ataxia is based upon clinical findings and confirmed by genetic testing.[4] Neuroimaging of the brain and spinal cord is recommended to exclude other causes of ataxia.[4] The neurological-exam-based Friedreich's Ataxia Rating Scale (FARS) was developed to assess the severity of ataxia symptoms.[10] The maximum score is 125 points based five sections that measure: bulbar function (score 0 to 11); upper limb coordination (score 0 to 36); lower limb coordination (score 0 to 16); peripheral nervous system function (score 0 to 26) and upright stability (score 0 to 36).[10,11] The interrater reliability of this tool was verified in 3 studies of patients with Friedreich's ataxia.[12-14] However, the minimal clinically important difference (MCID) for this assessment was never defined.[14] An assessment of the ability to complete activities of daily living (ADL) is part of the FAR scoring.[10] The FARS-ADL is a 9-question assessment which assesses 9 abilities: speech, swallowing, cutting food and handling utensils, dressing, personal hygiene, falling, walking, quality of sitting position, and bladder function.[10] Each component is scored between 0 and 4, with 0 being normal and 4 being worst.[10]

The modified FARS (mFARS) is another clinical assessment tool used to assess patient function and includes 4 of the 5 sections of the FARS: bulbar function, upper limb coordination, lower limb coordination, and upright stability.[2] Peripheral nervous system function is not measured in the mFAR scoring. The minimum score is 0 and the maximum score is 99.[2] A lower score indicates better neurological function and less physical impairment.[2] A reduction in FARS or mFARs signifies improved functioning.[10] An MCID for the mFARS has also not been determined. However, in a 5-year natural history study that included over 800 patients aged 4 to 80 years with Friedreich's ataxia, the mean progression in mFARS scores from baseline was 1.9 points by year one, 4.2 points by year 2, and 9.6 points by year 5.[13]

Management of Friedrich's ataxia is palliative and focused on symptomatic support from physical therapy, cardiology, endocrinology, neurology, and orthopedics to maintain optimal functioning as long as possible.[4] Until the recent FDA-approval of omaveloxolone, no medication has been approved to treat Friedrich's ataxia. Several ongoing investigational studies with antioxidants and gene therapy are assessing additional pathways besides Nrf2 signaling to treat Friedrich's ataxia and include targeting mitochondrial function or frataxin expression.[15]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Omaveloxolone is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.[1] Omaveloxolone oral capsules received FDA approval in February 2023 with priority review with orphan drug status and rare pediatric disease designation.[2] Omaveloxolone is an activator of nuclear factor (erythroid-derived 2) related factor signaling, which is involved in the cellular response to oxidative stress.[1] The recommended dose is 150 mg (3 capsules) once daily at least one hour before eating.[1]

The efficacy and safety of omaveloxolone to treat Friedreich's ataxia was evaluated in a 2-part, multi-center, placebo-controlled, double-blind, Phase 2 RCT (MOXIe).[2,3] The first part of this study was a 12-week dose escalation assessment in which various oral omaveloxolone doses ranging from 2.5 mg to 300 mg or placebo were administered to enrolled patients (n=69). Patients were split into 9 cohorts and randomized 3:1 to omaveloxolone (n=6) or placebo (n=2) at the specified dose for each cohort.[3] The primary efficacy outcome was change in peak work achieved during cardiopulmonary exercise testing on a stationary bicycle. No significant changes were observed in this endpoint, but improvements in the mFAR score were observed in a dose-dependent manner.[3] Patients treated with omaveloxolone 160 mg (n=4) demonstrated an improved mFAR score of 3.8 points from baseline ($p<0.001$) and a 2.3 point improvement in mFARS compared to patients taking placebo (n= 7; $p=0.06$) at 12 weeks.[3] The study was not powered to provide reliable results of efficacy.[10] Transaminase levels increased in a dose-dependent manner as well.[3] These increases were transient and no clinical evidence of hepatic injury was observed.[3]

In the second part of the study, 103 patients were randomized 1:1 to omaveloxolone 150 mg once a day (n=51) or placebo (n=52) for 48 weeks to evaluate safety and efficacy of omaveloxolone.[2] Because the drug is manufactured in 50 mg capsules, 150 mg was selected as the active comparator dose for ease of administration.[16] Enrolled patients were 16 to 40 years of age with genetically confirmed Friedreich's ataxia, a stable mFAR score between 20 and 80, able to swallow pills, and were able to complete maximal exercise testing on a recumbent stationary bicycle. These mFAR scores represented individuals just after time of presentation with Friedrich's ataxia in its mildest form and progression several years after loss of ambulation in a more severe form of Friedrich's ataxia.[2] Most of the patients (92%) were ambulatory. Patients with uncontrolled diabetes (HbA1c > 11%), significant cardiac disease (i.e., left-sided heart disease), active infection, clinically significant hepatic disease, and significant laboratory abnormalities (e.g., BNP > 200 pg/mL) were excluded from the study.[2] However, if patients developed diabetes or cardiac disease (i.e., arrythmias) during the trial, they were permitted to remain in the study.[2]

Patient with pes cavus, a musculoskeletal foot deformity characterized by high arch of the foot that does not flatten with weight bearing, may represent a subtype of Friedrich's ataxia. Presence of pes cavus may affect people's ability to use their legs, walk, and perform neurologic testing independent of their ataxia.[10] Patients with pes cavus were limited to 20% of the total study enrollment due to possible phenotypic differences.[2] Randomization was stratified by status of pes cavus (with pes cavus or without pes cavus).[2] In this RCT, 53% of enrolled patients were male, 97% were White, and the mean age was 24 years at study entry.[2] Baseline characteristics were slightly unbalanced between groups. Compared with the placebo cohort, the omaveloxolone cohort had patients with higher baseline mFAR scores, longer GAA repeat lengths and more advanced cardiac disease.[2]

The primary analysis was the change from baseline in the mFAR score for people who received omaveloxolone compared to placebo after 48 weeks of treatment in the full analysis population of patients (n=82) without pes cavus.[2] Previous studies have shown that patients with Friedrich's ataxia, on average, decline 1 to 2 points on the FAR clinical rating scale per year.[17] Based on these studies, improvement was defined by the investigators was a change in baseline mFAR score of 1.9 points or less.[2] At 48 weeks, low quality-evidence showed mean mFAR scores improved by 1.55 points from baseline in the omaveloxolone group and worsened by 0.85 points in the placebo group (mean difference between groups -2.4 points; 95% CI -4.3 to -0.5; $p=0.014$).[2] Omaveloxolone-treated patients had improvement from baseline in mFAR score by week 24 (mean change, -1.66; 95% CI not reported; $p=0.0191$). The investigators did not present statistical data for changes from baseline in the placebo group.

Secondary endpoints included change from baseline in Patient Global Impression of Change (PGIC), Clinician Global Impression of Change (CGIC), 9-hole peg test (assessment of hand coordination), 25-foot walk test, frequency of falls, work during maximal exercise testing, and FAR-ADL Score at 48 weeks.[2] The PGIC and CGIC are 7-point scales that assess improvement or worsening in symptoms from baseline.[10] Higher scores indicate worsening symptoms.[10] The key secondary endpoints PGIC and CGIC did not reach statistical significance in the full analysis population ($p=0.13$; $p=0.53$, respectively).[10] Secondary outcomes were analyzed in prespecified order as long as statistical evidence of benefit was continued to be shown.[10] No statistically significant changes between treatment groups were

noted in any of the other secondary outcomes except for the overall FAR-ADL score (placebo = 1.14 vs. omaveloxolone = -0.17; difference = -1.30; 95% CI not reported; p=0.042).[2] Very small improvements were observed in speech, swallowing, cutting food, personal hygiene, dressing, quality of sitting position, and walking in the omaveloxolone arm compared with placebo.[10] Falling and bladder function showed less worsening in the omaveloxolone arm compared to placebo arm.[10] None of the individual components showed statistically significant treatment differences between groups except for quality of sitting position (p=0.005).[10]

Limitations of this study include small sample size, modest duration for a life-long progressive disease, and possible limitations of the generalizability of the results (see **Table 4**).[2] The study endpoints were assessed individuals who could perform an exercise test and almost all patients were ambulatory (92%).[2] It is not clear how this medication would impact patients with severe Friedreich's ataxia that are unable to walk. The MOXIe trial excluded people under the age of 16 years. As a disease that is diagnosed in children in adolescents, data regarding the safety and efficacy in this population are clinically important. Although the trial had limitations and the effect size was relatively modest, Friedreich's ataxia is a slowly progressive disease, and small differences in functional progression over 1 to 2 years could translate to meaningful differences over the course of the disease.[2]

More data are needed from long term trials to evaluate sustainability of effect on neurologic improvement and adverse effects. An open-label, non-inferiority, 72-week extension study assessed the safety and tolerability of omaveloxolone in 149 patients who were enrolled in MOXIe Part 1 or Part 2.[10,18] Of these patients, 24 (16%) discontinued the open-label study and 125 (73%) completed the study.[10] The noninferiority testing demonstrated that the difference in mFARS between omaveloxolone and placebo observed at the end of placebo-controlled MOXIe part 2 (−2.17 ± 1.09 points) was preserved after 72 weeks in the extension (−2.91 ± 1.44 points).[18] The longer-term safety profile of omaveloxolone in the extension study was similar to that seen in MOXIe Parts 1 and 2, and omaveloxolone was generally well tolerated in the extension study.[18] No deaths were reported.[18] Serious adverse events were reported in 13 (8.7%) patients; of these, 8 (7.5%) individuals were in the placebo-omaveloxolone group and 5 (11.6%) were in the omaveloxolone-omaveloxolone group.[18] All of the serious adverse events were considered by the investigator to be unrelated to study drug, and none resulted in permanent discontinuation of study drug.[18]

Specific details from Part 2 of the MOXIe trial which contribute to the safety and efficacy data for Friedreich's ataxia are described and evaluated below in **Table 4**.

Clinical Safety:
The most common adverse effects of omaveloxolone observed in Phase 1 and Phase 2 clinical trials were transient increases in ALT (maximum increase was 2 times the upper limit of normal in 16% of patients), and AST (maximum increase was 5 times the upper limit of normal in 31% of patients), headache, nausea, abdominal pain, fatigue, diarrhea and musculoskeletal pain.[1] When the drug was discontinued, ALT and AST returned to normal values within 4 weeks and no cases of sustained hepatic injury were reported.[2] In part 2 of the MOXIe trial, increases in BNP above the upper limit of normal (100 pg/mL) in 14% of omaveloxolone-treated patients (compared with 4% of placebo-treated patients) were observed.[2] Overall, mean BNP values in omaveloxolone-treated patients remained below the upper limit of normal (<100 pg/mL) , and 2 (3.8%) patients had BNP values that exceeded 200 pg/mL.[2] Twenty-nine percent of omaveloxolone-treated patients reported elevated cholesterol levels above the usual limit in part 2 of the MOXIe trial.[2] The manufacturer recommends obtaining ALT, AST, bilirubin, BNP, and lipid parameters prior to initiating treatment and periodically during treatment.[1] Rate of adverse effects observed with omaveloxolone compared to placebo are presented in **Table 1**.

Table 1. Adverse Effects Reported in 10% or More of Patients Treated with Omaveloxolone and Greater than Placebo[1]

Adverse Effect	Omaveloxolone (n=51)	Placebo (n=52)
Elevated Liver Enzymes (ALT/AST)	37%	2%
Headache	37%	25%
Nausea	33%	13%
Abdominal Pain	29%	6%
Fatigue	24%	14%
Diarrhea	20%	10%
Musculoskeletal Pain	20%	15%
Oropharyngeal Pain	18%	6%
Influenza	16%	6%
Vomiting	16%	12%
Muscle Spasms	14%	6%
Back Pain	13%	8%
Decreased Appetite	12%	4%
Rash	10%	4%
Abbreviations: ALT = aminotransferase; AST = aspartate aminotransferase		

Omaveloxolone capsules should be taken on an empty stomach at least one hour before eating. It is important that patients prescribed omaveloxolone are able to swallow pills, as the capsules must be swallowed whole and should not be opened, crushed, or chewed.[1]

Guidance for Dosing Adjustments:

Hepatic Impairment

In patients with moderate hepatic impairment (Child-Pugh Class B) the omaveloxolone dose should be adjusted to 100 mg once daily.[1] If adverse effects emerge, further reduction to 50 mg once daily is recommended.[1] Omaveloxolone should not be administered to people with severe hepatic impairment (Child-Pugh Class C).[1]

Drug Interactions

- Strong CYP3A Inhibitors: Omaveloxolone maximum plasma concentration (Cmax) increased 3-fold and area under the curve (AUC) 4-fold following concomitant use with itraconazole (strong CYP3A inhibitor).[1]
- Moderate CYP3A Inhibitors: Omaveloxolone Cmax and AUC increased approximately 1.25-fold following concomitant use with verapamil (moderate CYP3A4 and P-gp inhibitor).[1]
- Strong and Moderate CYP3A Inducers: The effect of concomitant use with moderate and strong CYP3A4 inducers is unknown; however, a significant reduction in omaveloxolone exposure is likely following concomitant use based on its metabolic pathway.
- Certain CYP450 Enzymes or Transporter Substrates: omaveloxolone decreased the AUC of midazolam (CYP3A4 substrate) by approximately 45%, AUC of repaglinide (CYP2C8 substrate) by approximately 35%, and AUC of rosuvastatin (BCRP and OATP1B1 substrate) by approximately 30%.[1] There were no

clinically significant differences in the pharmacokinetics of digoxin (P-gp substrate) or metformin [(organic cation transporter (OCT)1 substrate] when co-administered with omaveloxolone.[1]

Look-alike / Sound-alike Error Risk Potential: No results available

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improvement in neurologic function (coordination, balance, speech)
2) Improvement in ability to complete activities of daily living
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in mFAR score from baseline at 48 weeks

Table 3. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	Omaveloxolone has been shown to activate the nuclear factor (erythroid-derived 2)-like 2 pathway, which is involved in the cellular response to oxidative stress.
Oral Bioavailability	Omaveloxolone C_{max} and $AUC_{0\text{-}inf}$ increased by approximately 350% and 15%, respectively, with a high-fat meal (compared to fasted conditions).
Distribution and Protein Binding	Mean volume of distribution = 7,361 Liters and protein binding = 97%
Elimination	Primarily hepatic: 92% of a single 150 mg dose is recovered in feces
Half-Life	Mean half-life: 57 hours (range: 32 to 90 hours)
Metabolism	Primarily metabolized by CYP3A with minor metabolism by CYP2C8 and CYP2J2 hepatic enzymes

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Lynch DR, et al.[2,10] MOXIe Study: Part 2 MC, DB, PC, PG, Phase 2 RCT	1. Omaveloxolone 150 mg orally once daily for 48 weeks 2. Placebo orally once daily for 48 weeks	Demographics: 1. Male: 53% 2. Mean age: 24 yo 3. White: 97% 4. Mean mFARS: 40 Key Inclusion Criteria: -Patients aged 16 to 40 years with genetically confirmed FA -mFARS score ≥ 20 and ≤ 80 Key Exclusion Criteria: -Uncontrolled diabetes (HbA1c > 11%) -Have a BNP > 200 pg/mL -History of significant cardiac ore hepatic disease -Taking substrates, inhibitors, or inducers of CYP3A4 or CYP2C8	ITT: 1. 51 2. 52 PP: 1. 44 2. 50 Attrition: 1. 7 (14%) 2. 2 (4%) FAS (patients without pes cavus): 1. 40 2. 42	Primary Endpoint: LSM change from baseline in mFARS score at 48 weeks in FAS 1. -1.55 +/- 0.69 2. 0.85 +/- 0.64 Difference: -2.41 95% CI -4.31 to -0.51 P=0.014 Secondary Endpoints: 1. LSM change in PGIC from baseline at 48 weeks 1. 3.89 2. 4.32 Difference: -0.4.3 P=0.13 2. LSM change in CGIC from baseline at 48 weeks 1. 3.92 2. 4.06 Difference: -0.13 P=0.53 95% CI NR 3. LSM change in performance on 9-hole peg test from baseline at 48 weeks 1. -0.0014 2. -0.0001 LSM Difference: -0.0013 P=0.18 95% CI NR 4. LSM change in performance on the 25-foot time walk test	NA NS NS NS NS	Any SAE: 1. 5 (10%) 2. 3 (6%) Discontinuation due to AE: 1. 4 (8%) 2. 2 (4%) Increased ALT: 1. 19 (37%) 2. 1 (2%) Increased AST: 1. 11 (22%) 2. 1 (2%) p-value and CI NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1 via IWRS. Small sample size may have introduced bias (103 recruited, full analysis population limited to 82 people without pes cavus). Baseline characteristics were slightly unbalanced. The omaveloxolone cohort had more advanced disease, higher baseline mFAR scores, longer GAA repeat lengths and more patients with a history of cardiomyopathy. It is not clear if patients with less advanced disease would response favorably to treatment. Performance Bias: Unclear. Study medication and placebo were identical in appearance. However, adverse effects may have resulted in unblinding. Detection Bias: Low. Sponsor, investigators, and patients were blinded to treatment assignment. Attrition Bias: High. Attrition was higher in the active treatment arm due to adverse effects and withdrawal of consent. Not clear how missing data was handled. Reporting Bias: High. Study protocol was unavailable. Secondary outcomes analyzed in prespecified order as long as statistical evidence of benefit was continued to be shown. If not significant, statistical testing was stopped. Other Bias: High. Study was sponsored and funded by drug manufacturer. Four authors are employees of the manufacturer. **Applicability**: Patient: Drug studied in FA patients with moderate impairment. Not clear how patients with severe impairment would respond to this therapy. Only studied in people aged ≥16 yo. As a pediatric condition, the role of omaveloxolone in managing FA in children is of greater interest. Non-white populations were not represented in the study; this undermines confidence in this evidence applies communities served by OHP. Intervention: 150 mg daily was the dosing approved by FDA for the FA indication. Comparator: As no other medications are approved for FA, placebo was an appropriate comparison. Outcomes: mFARs has been validated, but MCID has not been determined. Investigators relied upon historical data to determine threshold for clinical improvement.

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				from baseline at 48 weeks 1. -0.0169 2. -0.0226 LSM Difference: 0.0058 P=0.46 95% CI NR 5. LSM change in frequency of falls from baseline at 48 weeks: LSM Difference: -0.32 1. 3.0 2. 8.5 P=0.28 95% CI NR 6. LSM Change in FAR-ADL from baseline at 48 weeks 1.-0.17 2. 1.14 LSM Difference: -1.30 P=0.04 95% CI NR	NS			Setting: 7 sites in US, 3 sites in Europe, and 1 site in Australia

Abbreviations AE = adverse effect; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = aspartate aminotransferase; BNP = beta natriuretic peptide; CGIC = Clinical Global Impression of Change; CI = confidence interval; DB = double blind; FA = Friedreich's ataxia; FAR-ADL = Friedreich's Ataxia Rating-Activities of Daily Living; FAS = full-analysis set; GAA = guanine-adenine-adenine; HbA1c = hemoglobin A1c; ITT = intention to treat; IWRS = interactive web response system; MC = multi-center; MCID = minimal clinically important difference; mFARS = modified Friedreich's Ataxia Rating Scale; LSM = least squares mean; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OHP = Oregon Health Plan; PC = placebo controlled; PG = parallel group; PGIC = Patient Global Impression of Change; PO = orally; PP = per protocol; RCT = randomized controlled trial; SAE = serious adverse effect; yo = years old

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SKYCLARYS safely and effectively. See full prescribing information for SKYCLARYS.

SKYCLARYS™ (omaveloxolone) capsules, for oral use
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
SKYCLARYS is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- Obtain alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, B-type natriuretic peptide (BNP), and lipid parameters prior to initiating SKYCLARYS and during treatment. (2.1, 5.1, 5.2, 5.3)
- Recommended dosage is 150 mg (3 capsules) taken orally once daily. (2.2)
- Administer SKYCLARYS on an empty stomach at least 1 hour before eating. (2.2)
- Swallow SKYCLARYS capsules whole. Do not open, crush or chew. (2.2)
- Moderate and Severe Hepatic Impairment: The recommended dosage of SKYCLARYS is 100 mg once daily for patients with moderate hepatic impairment. If adverse reactions emerge, further reduce the dosage to 50 mg once daily. Avoid use in patients with severe hepatic impairment. (2.5, 8.6, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 50 mg (3)

----------CONTRAINDICATIONS----------
None. (4)

----------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. (2.1, 5.1)
- Elevation of B-type Natriuretic Peptide (BNP): Advise patients of signs and symptoms of fluid overload. (2.1, 5.2)
- Lipid Abnormalities: Monitor cholesterol periodically during treatment. (2.1, 5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥20% and greater than placebo) are elevated liver enzymes (AST/ALT), headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Reata Pharmaceuticals, Inc. at 1-800-314-3934 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Moderate or Strong CYP3A4 Inhibitors: Avoid concomitant use. Consider SKYCLARYS dosage reduction with monitoring if use is unavoidable. (2.4, 7.1)
- Moderate or Strong CYP3A4 Inducers: Avoid concomitant use. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2023

Appendix 2: Proposed Prior Authorization Criteria

Omaveloxolone (SKYCLARYS™)

Goal(s):

- Promote use that is consistent with medical evidence and product labeling in patients with Friedreich's ataxia.

Length of Authorization:

- Up to 12 months

Requires PA:

- Omaveloxolone oral capsules (pharmacy claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Recommended Dosage of Omaveloxolone with Concomitant use of CYP3A4 Inhibitors or Inducers

Concomitant Drug Class	Dosage
Strong CYP3A4 Inhibitor (such as, but not limited to: ketoconazole, nefazodone, voriconazole)	Recommended to avoid concomitant use. If co-administration cannot be avoided: • Reduce omaveloxolone dose to 50 mg once daily with close monitoring to detect adverse effects • If adverse effects emerge, coadministration with strong CYP3A4 inhibitor should be discontinued
Moderate CYP3A4 Inhibitor (such as, but not limited to: erythromycin, verapamil, diltiazem, cyclosporine)	Recommended to avoid concomitant use. If co-administration cannot be avoided: • Reduce omaveloxolone dose to 100 mg once daily with close monitoring to detect adverse effects • If adverse effects emerge, further reduce omaveloxolone dose to 50 mg once daily
Strong or Moderate CYP3A4 Inducer (such as, but not limited to: phenytoin, carbamazepine, rifampin)	Recommended to avoid concomitant use.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this for an FDA-approved indication for a patient 16 years of age and older?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Have baseline labs (ALT, AST, bilirubin, BNP and lipid parameters) been obtained prior to initiating therapy?	**Yes:** Document date and results here: _____ _____ _____ Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is baseline BNP > 200 pg/mL?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Has the provider documented the patient does not have severe hepatic impairment (Child-Pugh Class C)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. If patient has moderate liver impairment (Child-Pugh Class B) has the dose been modified to 100 mg once daily?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. If patient is taking other medications, are they CYP3A4 inhibitors or inducers that require omaveloxolone dosing adjustments as outlined in Table 1 and has the omaveloxolone dose been adjusted?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement.	**Yes:** Approve for 12 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 6/23 (DM)
Implementation: TBD