CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216718
PDUFA Goal Date	February 28, 2023
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Reviewer Name(s)	Carla Darling, PharmD, BCPS
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Review Completion Date	February 27, 2023
Subject	Evaluation of Need for a REMS
Established Name	Omaveloxolone
Trade Name	Skyclarys
Name of Applicant	Reata Pharmaceuticals Inc.
Therapeutic Class	Nuclear factor erythroid 2-related factor 2 (Nrf2) activator
Formulation(s)	50 mg oral capsules
Dosing Regimen	150 mg by mouth once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Skyclarys (omaveloxolone) is necessary to ensure the benefits outweigh its risks. Reata Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application (NDA) 216718 for omaveloxolone with the proposed indication for the treatment of Friedreich's ataxia (FA). The key risks associated with omaveloxolone include elevations in liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transferase [GGT]), B-natriuretic peptide (BNP) and N-Terminal Prohormone of B-Type Natriuretic Peptide (NT-Pro BNP). The applicant did not submit a REMS with this application but submitted an enhanced pharmacovigilance plan.

FA is a rare, genetic, progressive, neurodegenerative disorder that affects children and adults.[1] Patients have a shortened life expectancy with the most common causes of death from cardiovascular complications such as heart failure and arrhythmias. There are no available approved therapies for the treatment of FA; therefore, there is an unmet need. If approved, omaveloxolone would be the first approved therapy for the treatment of FA.

DRM and the Division of Neurology 1 (DN1) have determined that a REMS is not needed to ensure the benefits of omaveloxolone outweigh its risks. The efficacy of omaveloxolone was evaluated in one pivotal phase 2 trial. The clinical reviewer determined that the applicant provided substantial evidence of effectiveness for omaveloxolone based on a single study and confirmatory evidence.[2]

Based on the safety and efficacy information available, a REMS is not necessary to ensure the benefits outweigh the risks of omaveloxolone. The most important safety concerns identified with the use of omaveloxolone include increases in liver enzymes (AST, ALT and GGT) as well as BNP and NT-Pro BNP. Labeling will include BNP level elevations observed with omaveloxolone and recommendations for monitoring for fluid overload and cardiac failure as well as notes that it is unclear if elevations in BNP in the clinical trial are related to omaveloxolone or the disease state. Prescribers are likely familiar with cardiovascular risks and appropriate monitoring and management in FA patients as this this is a common outcome of the disease.[1] Liver enzyme elevations will also be communicated in labeling including recommendations for monitoring and management. If approved, labeling would include Warnings and Precautions to communicate the risks of BNP (b) (4) as well as liver enzyme (AST and ALT) elevations. At the time of this review, final labeling, and post-marketing requirements (PMRs) were still under negotiation. If new safety information becomes available, DRM can re-evaluate the need for a REMS.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Skyclarys (omaveloxolone) is necessary to ensure the benefits outweigh its risks. Reata Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application (NDA) 216718 for omaveloxolone with the proposed indication for the treatment of

Friedreich's ataxia (FA).[3,4] This application is under review in the Division of Neurology 1 (DN1). The Applicant did not submit a REMS with this application but proposed an enhanced pharmacovigilance plan to provide expedited reporting to FDA for adverse events of interests, laboratory abnormalities, and body measurements of interests.[5]

2. Background

2.1. Product Information

Skyclarys (omaveloxolone), a nuclear factor erythroid 2-related factor 2 (Nrf2) activator, is a new molecular entity[a], proposed for the treatment of FA. Omaveloxolone binds to Kelch-like ECH-associated protein 1 (Keap1) resulting in activation of the transcription factor Nrf2 (b) (4)Nrf2 is a transcription factor that modulates the expression of genes that protect the cell by regulating mitochondrial function, oxidative stress, and inflammation.[7] Omaveloxolone activation of the Keap1-Nrf2 pathway is thought to prevent cellular death, while restoring Nrf2 and promoting mitochondrial bioenergetic, antioxidative, and anti-inflammatory activities (b) (4)[9]

Omaveloxolone is proposed as 50 mg oral capsules. The proposed dosage is 150 mg orally once daily on an empty stomach at least 1 hour before eating. Omaveloxolone is likely to be administered primarily in the outpatient setting for the chronic treatment of FA.[b] Omaveloxolone was granted orphan drug designation and fast track designation. Omaveloxolone is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216718 relevant to this review:

- **06/19/2017:** Orphan drug designation granted for the treatment of Friedreich's ataxia.
- **08/31/2021:** Applicant informed at pre-NDA meeting via teleconference that the Agency had insufficient information to comment on the Applicants proposed risk management plan and that the need for a REMS would be determined during the review of the application.
- **11/17/2021:** Fast track designation granted.
- **01/28/2022:** Part 1 (Modules 1, 2, 4, 5) of NDA 216718 submission for the treatment of Friedreich's ataxia received.[4]
- **03/30/2022:** The final portion of the rolling submission (Part 2 containing Module 3) for NDA 216718 received.[3]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- **07/14/2022:** A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the safety review was ongoing, including evaluation of cardiac safety.[10]
- **08/08/2022:** The Agency issued a Major Amendment Acknowledgement Letter to the Applicant extending the PDUFA goal date by 3 months after receipt of submissions with additional data and analyses for efficacy and safety.[11]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

FA is a rare, genetic, progressive, neurodegenerative disorder that affects children and adults. The prevalence is about 1 in 30,000 to 50,000 people worldwide.[1,12,c] The Applicant estimates that FA affects about 5,000 patients in the United States and 22,000 globally.[13,14]

FA is an autosomal recessive disorder caused by mutations in the frataxin gene resulting in reduced transcription of frataxin.[1] In most cases the disorder is caused by a trinucleotide (GAA) repeat expansion in the first intron of the frataxin gene. Frataxin is a protein involved in normal mitochondrial function and appears to have a role with iron-sulfur cluster biogenesis, iron chaperoning, iron detoxification, antioxidation, and regulation of iron storage.[1,15] Frataxin deficiency may lead to mitochondrial accumulation of iron, oxidative stress, and mitochondrial dysfunction which contribute to the clinical features of FA.[15,16]

The typical age of onset occurs between 5 to 15 years.[16] Clinical manifestations include neurologic features such as progressive limb and gait ataxia, sensory neuropathy, dysarthria, weakness, ocular fixation instability, visual and hearing impairment and non-neurologic features such as kyphoscoliosis, foot deformities, increased risk of diabetes mellitus, cardiomyopathy, and arrythmias.[1,17] The clinical course is characterized by a progressive loss of the ability to ambulate and most patients are wheelchair-dependent by their mid-20s.[1]

The diagnosis has a significant impact on life expectancy and quality of life.[d] Patients have a shortened life expectancy with an average age of death of 37.5 years.[1,18] The most common causes of death are due to cardiovascular complications such as heart failure and arrhythmias.[1]

3.2. Description of Current Treatment Options

There are no available approved therapies for the treatment of FA. The current management options treat symptoms and complications rather than targeting the underlying disorder and slowing disease progression. Depending on the patients presentation and complications, management involves a

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

multidisciplinary team that may include neurologists; physical, occupational, and speech therapists; cardiologists; endocrinologists; ophthalmologists; and orthopedic specialists.[1] Possible options used off-label for treatment include iron chelators and vitamin supplements. There is a significant unmet need for effective treatment options for FA.

4. Benefit Assessment

The efficacy of omaveloxolone for the treatment of Friedreich's ataxia was evaluated in Study 408-C-1402 (National Controlled Trial 02255435, hereafter referred to as Study 1402). Study 1402 was a phase 2, randomized, double-blind, placebo-controlled, multicenter trial in patients with FA that consisted of 2 parts and was followed by an open-label extension with up to 3 years of omaveloxolone exposure. Part 1 of the study was a dose-escalating phase evaluating omaveloxolone doses 2.5 mg to 300 mg. Part 2 further evaluated omaveloxolone 150 mg and was the main study supporting the efficacy of omaveloxolone in FA patients. Eligible patients in part 2 of Study 1402 included males and females ages 16 to 40 years who were able to complete maximal exercise testing, had genetically confirmed FA with baseline modified Friedreich's Ataxia Rating Scale (mFARS) scores between 20 and 80, and a left ventricular ejection fraction of at least 40%.[6,19] Patients with or without pes cavus defined as having a loss of lateral support were included in Study 1402 part 2. [e] Patients with significant baseline CV disease or with BNP levels greater than 200 pg/mL were excluded in Study 1402. An open label extension study (Study 1402 Extension) is ongoing for patients who completed Study 1402.[9]

Study 1402 part 2 evaluated omaveloxolone 150 mg by mouth daily compared to placebo over 52 weeks (48 weeks on treatment and 4 weeks off treatment). A total of 103 subjects were randomized 1:1 to placebo (N=52) or omaveloxolone (N=51) orally once daily. Randomization was stratified by pes cavus status (with or without pes cavus). The protocol specified a maximum of 20% of subjects could have pes cavus. The primary efficacy endpoint was the change in the mFARS score from baseline to Week 48 compared to placebo in patients without pes cavus (N=82).[2] The mFARS consists of 4 domains that evaluate bulbar function, upper limb coordination, lower limb coordination, and upright stability, and each domain consists of several elements. The mFARS has a maximum score of 99, with a higher score on the mFARS signifying greater physical impairment. The key secondary endpoints were patient global impression of change (PGIC) and clinical global impression of change (CGIC) at Week 48. Five additional secondary endpoints in hierarchical order include 9-hole peg test (9-HPT), 25-foot walk test (25FWT), frequency of falls, peak work during maximal exercise, Friedreich's Ataxia-activities of daily living (FA-ADL).

The primary efficacy analysis in Study 1402 part 2 showed a statistically significant lower mFARS scores at week 48 in the omaveloxolone treatment group (N=40) compared to placebo (N=42) with a least square (LS) mean difference between treatment groups of -2.41 (95% confidence interval [CI]: -4.32, -0.51); p=0.014. The key secondary endpoints, PGIC and CGIC scores at Week 48, were not statistically different for omaveloxolone compared with placebo. Four out of the five additional secondary

[e] Per the Applicant, patients with pes cavus have musculoskeletal foot deformity and may represent a different subtype of FA that may have a different pathophysiology and clinical phenotype.

endpoints were not statistically significant except for FA-ADL score at week 48, which showed improvement from baseline with omaveloxolone treatment compared to placebo.

Overall, the single small study, with lack of adequate support from secondary endpoints, does not appear robust enough to independently provide substantial evidence of effectiveness. The clinical reviewer determined that Study 1402 part 1 provides confirmatory evidence of effectiveness for omaveloxolone in the treatment of FA based on observed dose dependent increases in ferritin. Nrf2 activation from omaveloxolone doses 5 mg to 300 mg appear to increase ferritin, which can be suggestive of a pharmacodynamic effect of omaveloxolone treatment.

Two post-hoc analyses were submitted by the Applicant as supportive evidence for efficacy. The first is a delayed start analysis in patients from the ongoing Study 1402 Extension. The second is a propensity matched analysis of patients in the natural history study, Friedreich's Ataxia Clinical Outcome Measures (FA-COMS) study (National Controlled Trial 03090789), compared to omaveloxolone treated patients from the Study 1402 Extension. The clinical reviewer concluded that the post-hoc delayed start analysis was uninterpretable and not supportive. The propensity matched analysis did provide confirmatory evidence of effectiveness, which showed a statistically significant difference in mFARS change from baseline between Study 1402 Extension and FA-COMS in favor of omaveloxolone treated patients.[2]

Overall, the clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness based on the effect of omaveloxolone in improving mFARS scores in Study 1402 part 2, and the confirmatory evidence from the post-hoc natural history comparison and Study 1402 part 1.[2, f]

5. Risk Assessment & Safe-Use Conditions

A total of 392 patients have been exposed to omaveloxolone across multiple clinical development programs for varying indications.

The primary safety population consisted of 165 patients with Friedreich's ataxia from Study 1402, including 137 patients exposed to omaveloxolone 150mg daily for at least 48 weeks and 112 patients exposed for at least 96 weeks. Additional supportive data is available from Study 1402 Extension to inform long-term safety. DN1 identified an imbalance in discontinuations at week 48 in Study 1402 of 7 (14%) patients treated with omaveloxolone compared to 2 (4%) patients on placebo, which could introduce bias to the study outcome in a small study. However, the clinical reviewer states that the direction of the bias in each group and its overall effect on the primary results are unclear. [2]

The most common adverse reactions in Study 1402 (≥18%) were elevated liver enzymes (ALT and AST), headache, nausea, abdominal pain, fatigue, diarrhea, musculoskeletal pain, and oropharyngeal pain.

Cardiovascular and hepatic safety were topics of interest identified by the applicant and are discussed in more depth below (see Section 5.2).

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5.1. Serious Adverse Events[g]

Eight (8) patients, 5 patients treated with omaveloxolone and 3 patients on placebo, experienced serious adverse events (SAE). No SAEs were reported by more than 1 patient during the 48-week treatment period except for atrial fibrillation which was reported in 1 patient in each treatment group. Additional SAEs reported in omaveloxolone treated patients include anemia (1), ventricular tachycardia (1), craniocerebral injury (1), and palpitations, sinus tachycardia, and musculoskeletal pain which were reported in the same patient. Overall, the clinical reviewer concluded that the anemia and craniocerebral injury are unlikely related to omaveloxolone treatment and that the determination of cardiac involvement due to study drug is complicated by comorbidities in FA patients. Cardiovascular safety is discussed in more depth below (see Section 5.2.1).

There were no deaths reported in the clinical study for the treatment of FA.

5.2. Adverse Events of Special Interest

5.2.1. Elevation of Aminotransferases

Hepatic safety was an adverse event of interest in the clinical development program as transient elevations were observed in other omaveloxolone clinical trials.[19] In Study 1402 omaveloxolone caused elevations in liver transaminases (AST, ALT, and GGT) without increases in bilirubin.[2] A total of 31%, 16% and 4% of patients in the omaveloxolone group exceeded the threshold criterion of ALT or AST >3× the upper limit of normal (ULN), >5x ULN or >10x the ULN, respectively compared to none in placebo group. [h] Hy's Law criteria was not met in any patient in the study. Mean increases observed in ALT, AST and GGT induced by omaveloxolone were maximal at Week 2 and then gradually returned to baseline. Per the clinical reviewer, transaminase elevations appear reversible with or without clinical interventions such as drug discontinuation. Per the Applicant, the elevations in ALT, AST, and GGT are hypothesized to be related to the mechanism of action of omaveloxolone and not associated with liver injury.[19]

DN1 consulted the Office of Clinical Pharmacology, Division of Applied Regulatory Science (DARS) to verify and comment on the accuracy these claims.[8] In brief, the DARS review team stated that Nrf2 activation has been shown to induce GGT and ferritin protein expression. In addition, other Nrf2 activators (e.g., bardoxolone methyl and oltipraz) caused increases in transaminases without increases

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[h] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

in bilirubin. DARS referenced studies that show Nrf2 activators as hepatoprotective in rodent models of drug of chemical induced liver injury through effects on antioxidant stress responses. The DARS review team concluded that based on *in vitro,* animal, and clinical studies, it appears that increased levels of liver transaminases following omaveloxolone is a pharmacodynamic effect related to Nrf2 activation rather than liver toxicity.

In addition, DN1 consulted the Division of Hepatology and Nutrition (DHN), Drug-Induced Liver Injury (DILI) Team, to review the risk of drug-induced liver injury given the increases in ALT, AST, and GGT during the trial.[7] DILI team review states that non-clinical data do not suggest a strong risk for DILI, there were no Hy's law cases or cholestatic injury cases in the clinical trials, and benign gene expression with modest DILI adaptation is a plausible cause for aminotransferase elevations. The DILI team concluded that there is no strong evidence for a strong DILI signal with omaveloxolone; however, due to the small sample size in the omaveloxolone trials, the risk for clinically significant or serious DILI may appear in a larger post-market population. DILI team recommends communicating liver enzyme elevations in labeling including monitoring and management recommendations. Post-market studies to further characterize acute and chronic liver injury were also recommended.

The clinical reviewer concluded that there were no cases of jaundice, Hy's law or cholestatic liver injury with omaveloxolone; however, the clinical database is too small to detect significant DILI with omaveloxolone. The clinical reviewer determined that liver enzyme elevations (AST and ALT) can be communicated in labeling.[2] The current draft label includes elevation of aminotransferases in Section 5, Warning and Precaution.[6] The label provides recommendations for monitoring and management.

5.2.1. Cardiovascular (CV) Safety

CV safety was an adverse event of interest in the clinical development program as FA is associated with cardiac complications and cardiomyopathy is one of the major causes of death.[1] Additionally, another Nrf2 activator, bardoxolone methyl (NDA 215484), that was studied in patients with chronic kidney disease caused by Alport syndrome was associated with CV risks of heart failure and increased blood pressure.[20]

DN1 consulted the Division of Cardiology and Nephrology (DCN) to review the cardiac safety of omaveloxolone.[21] DCN reviewed cardiovascular events reported in Study 1402. In brief, DCN identified a higher proportion of patients in the omaveloxolone treatment group (49%) that reported a history of cardiomyopathy compared to placebo (29%). The incidence of CV events in Study 1402 were similar across the treatment groups (omaveloxolone 28% and placebo 29%).[i] The estimated annualized rate of CV events per 100-person years was 32 per 100 patient years in the placebo group and 33 per 100 patient years in the omaveloxolone group. Most patients had BNP levels within normal limits during the trial. Elevations in BNP levels greater than 100 pg/L occurred more frequently in the omaveloxolone

[i] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

(20%) group compared to placebo (6%) during the trial.[j] There were no observed increases from baseline in clinically monitored blood pressure; however, the DCN reviewer cautions this trial was small and not powered to detect small changes that could be clinically meaningful and concluded that the safety database was too small to characterize CV safety of omaveloxolone in patients with FA. Additional challenges for assessment of CV safety data included a higher baseline history of CV events and cardiomyopathy in the omaveloxolone group compared to placebo and the high background rate of cardiomyopathy and arrhythmias in patients with FA. The DCN reviewer also raised concerns about the BNP level elevations and its potential risk for adverse cardiac effects with omaveloxolone treatment given the similarities to the other Nrf2 activator bardoxolone.

The clinical reviewer concluded that BNP and NT-Pro BNP elevations can be communicated in labeling.[2] The current draft label includes elevation of BNP in Section 5, Warnings and Precautions and notes that it is unclear if elevations in BNP in the clinical trial are related to omaveloxolone or the disease state. Labeling also includes recommendations for monitoring for fluid overload and cardiac failure.[6]

6. Expected Postmarket Use

The anticipated prescribing population for omaveloxolone will likely be adult and pediatric neurologists with experience in treatment of FA. Across the United States, treatment centers with expertise in the treatment of FA are available. Management also involves a multidisciplinary team of specialists, including cardiologists who would be involved in monitoring for cardiovascular risks. Omaveloxolone is proposed as oral capsules and will likely be administered by patients/caregivers primarily in the outpatient setting. If approved, this would be first treatment option approved for FA.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not submit a REMS with this application.

7.1. Other Proposed Risk Management Activities

The Applicant's submission includes a Pharmacovigilance plan that proposes enhanced pharmacovigilance with expedited reporting for the following: cases of possible DILI, Hy's law, reports of liver failure or transplant; significant elevations of liver enzymes; congestive heart failure and related deaths; and significant weight loss or decrease in body mass index. Additionally, the Applicant proposes

[j] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

a Patient Support Program of trained registered nurses and a patient safety registry for up to 5 years post-approval to provide long-term safety data.[5]

Reviewer's Comments: *We note that these other activities proposed by the Applicant are voluntary risk management activities, we defer to the Division of Pharmacovigilance and Division of Epidemiology for review and input.*

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of omaveloxolone based on the efficacy and safety information currently available. FA is a rare, genetic, progressive, neurodegenerative disorder that affects children and adults. Patients have a shortened life expectancy where the most common causes of death are from cardiovascular complications such as heart failure and arrhythmias. There are no available approved therapies for the treatment of FA; therefore, there is an unmet need. If approved, omaveloxolone would be the first approved therapy for the treatment of FA.

Study 1402 part 2 was the main study supporting the efficacy of omaveloxolone in FA patients and showed a statistically significant lower mFARS scores at week 48 compared to placebo. Overall, the clinical reviewer determined that the single small study, with lack of adequate support from secondary endpoints, does not appear robust enough to independently provide substantial evidence of effectiveness. Study 1402 part 1 provided confirmatory evidence of effectiveness with pharmacodynamic data supporting the biologic plausibility of the treatment effect. In addition, the ad-hoc natural history comparison provided confirmatory evidence of lower mFARS score observed in the omaveloxolone study versus the FA-COMS data. The Division of Neurology 1 determined that Applicant provided substantial evidence of effectiveness based on a single study and confirmatory evidence.

The most important safety concerns identified with the use of omaveloxolone include increases in liver enzymes (AST, ALT and GGT) as well as BNP and NT-Pro BNP. Omaveloxolone is associated with elevations in liver transaminases (AST, ALT, and GGT) without increases in bilirubin, which has also been observed in the clinical development program for other Nrf2 activators including bardoxolone methyl. These elevations in liver transaminases appear to be transient and return to baseline with or without stopping omaveloxolone. There was no evidence in the clinical development program to suggest that the risk may be detected early to prevent worsening or that there is an effective strategy to prevent worsening as enzyme elevations appear to decrease with or without discontinuing the drug. Important sequelae of elevations in liver transaminases includes hepatotoxicity; however, there were no Hy's law or DILI cases, therefore, a strategy to reduce severity or long-term negative impact of these outcomes was not considered. The review team had concerns that the size of Study 1402 was too small to detect a significant drug-induced liver injury with omaveloxolone and recommended labeling for monitoring as well as post-market acute and chronic studies to further assess DILI. Liver transaminase elevations will be communicated in Section 5, Warnings and Precautions of the label. Labeling is expected to include recommendations for monitoring and management of liver transaminase elevations.

Elevations in BNP levels observed with omaveloxolone treatment may be associated with adverse cardiac effects such as cardiac complications and cardiomyopathy. However, given that FA patients have a risk of cardiac failure, it is unclear whether the risk increases with omaveloxolone treatment. Furthermore, elevations in BNP were observed in patients with and without history of cardiomyopathy. Prescribers are likely familiar with the risk of cardiac failure in FA patients as this is a common outcome of the disease.[1] BNP elevations will be communicated in Section 5, Warnings and Precautions of the label. Labeling is expected to include recommendations for BNP monitoring.

Overall, the clinical reviewer concludes that the safety profile of omaveloxolone for the treatment of FA is acceptable. Based on the data available and that the prescribing community should be familiar with the risk of cardiac failure in FA patients, this reviewer concluded that if omaveloxolone should be approved, a REMS is not necessary to ensure the benefits outweigh the risks. At the time of this review, final labeling and post-marketing requirements (PMRs) were still under negotiation.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary for Omaveloxolone to ensure the benefits outweigh the risks. In general, healthcare providers who treat FA are expected to be familiar with the risk of cardiac failure and the importance of patient monitoring. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

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