CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216718Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Memorandum Regarding Real World Evidence

Date:	February 27, 2023
Reviewer:	Catherine Callahan, PhD, MA Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
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Subject:	Review of natural history study as confirmatory evidence for the efficacy of omaveloxolone for treatment of Friedreich's ataxia
Drug Name:	Omaveloxolone
Application Type/Number:	NDA 216718
Applicant:	Reata Pharmaceuticals, Inc.
OSE RCM #:	2022-2196

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EXECUTIVE SUMMARY

The purpose of this memo is for the Division of Epidemiology 1 (DEPI-I) to document our input) regarding the natural history study submitted as confirmatory evidence for approval of omaveloxolone for treatment of Friedreich's ataxia (FA).

The Sponsor submitted a new drug application (NDA) for omaveloxolone on March 30, 2022. The Sponsor's initial submission included Study 1402 Part 1, Part 2, and extension as the primary clinical evidence to support this submission. During the midcycle teleconference between the Sponsor and FDA on July 14, 2022, the Division of Neurology 1 (DN1) conveyed concerns regarding the strength of efficacy evidence.[a] During the midcycle teleconference, the Sponsor stated that they had more recent data from the ongoing open-label extension study and natural history comparisons to provide additional data at the later time points.

The Sponsor presented a post hoc comparative analysis of an ongoing extended access study of omaveloxolone treatment and an observational study of FA (FA-COMS). Study 1402 extension is an ongoing, extended access study designed to provide treatment with omaveloxolone (150 mg/day) to eligible patients with FA following completion of study 1402 Part 1 or Part 2 while collecting safety and tolerability data. Data from Study 1402 Part 1 and Study 1402 Part 2 were not included in this propensity matched analysis. Only data from Study 1402 Extension were compared to natural history data. The Clinical Outcome Measures in FA (FA-COMS) study is a global, multi-center, longitudinal, prospective observational study that has enrolled more than 1,000 patients, with follow-up as long as 19 years in some patients. Clinical outcome measures, including Friedreich's Ataxia Rating Scale (FARS) and modified Friedreich's Ataxia Rating Scale (mFARS), are assessed annually.

For the primary endpoint, change in mFARS at Year 3, in the Pooled Primary Population, matched FA-COMS patients progressed 6.611 mFARS points whereas patients treated with omaveloxolone in Study 1402 Extension progressed 3.004 points (difference = -3.607 points; nominal p=0.0001, Appendix Table 2).

Overall, the comparative analysis presented by the Sponsor has limitations expected in a study using an external comparator (e.g., uncontrolled confounding, selection bias, loss to follow-up). The analysis was conducted post hoc and did not follow the FDA guidelines regarding transparency for using real-world data. However, this study did have the strengths of individual-level data which allowed for propensity matching and adjustment for age (one of the strongest predictors of FA progression).

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[a] NDA 216718 Mid-Cycle Communication DARRTS Reference ID: 5029547

1 INTRODUCTION

The purpose of this memo is for the Division of Epidemiology 1 (DEPI-I) to provide input regarding the natural history study submitted as confirmatory evidence for approval of omaveloxolone for treatment of Friedreich's ataxia (FA).

Omaveloxolone is currently under review by the Division of Neurology 1 (DN1) for the proposed indication of FA. FA is an ultra-rare, genetic, rapidly progressive neurodegenerative disorder that affects approximately 5,000 patients in the United States and 22,000 patients globally. There are currently no approved therapies for FA.[b]

Omaveloxolone (also known as RTA 408) is a novel, orally bioavailable, semi-synthetic oleanane triterpenoid compound that activates the transcription factor nuclear factor, erythroid 2 like 2 (Nrf2), which regulates the response to cellular oxidative stress and coordinates the expression of genes that normalize mitochondrial function, restore redox balance, and reduce inflammation.[c]

The Sponsor submitted a new drug application (NDA) for omaveloxolone on March 30, 2022. The Sponsor's initial submission included Study 1402 Part 1, Part 2, and extension as the primary clinical evidence to support this submission.

During the midcycle teleconference between the Sponsor and FDA on July 14, 2022, the DN1 conveyed concerns regarding the strength of efficacy evidence.[d] Specifically:

- "The pivotal study, Study 408-C-1402 Part 2, is not exceptionally persuasive and has only weak support from the secondary endpoints.
- The significant reduction in the number of subjects in the extension phase at each time point makes it challenging to interpret the delayed start analyses.[e]
- There is a lack of support from Study 408-C-1402 Part 1 as no dose-response relationship was observed.
- Additional justification or literature is needed to support the relevance of the biomarkers (b) (4) (i.e., ferritin, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)) to Nrf2

[b] NDA 216718 Reviewer's guide

[c] Ibid

[d] NDA 216718 Mid-Cycle Communication DARRTS Reference ID: 5029547

[e] The delayed start analysis refers to a post-hoc analysis with the objective of determining if omaveloxolone had a persistent effect on FA disease progression to assess if the benefit cannot be recovered by patients who start omaveloxolone later in time. The placebo-corrected difference in the "delayed-start period" (Study 1402 Extension Week 72 change from baseline mFARS values) was compared to the placebo-corrected difference in the "placebo-controlled period" (Study 1402 Part 2 Week 48 change from baseline mFARS values).

activation and how that would correlate with treatment benefit in FA patients."

During the midcycle teleconference, the Sponsor stated that they had more recent data from the ongoing open-label extension study and natural history comparisons to provide additional data at the later time points. DN1 stated they were open to reviewing the updated analysis, time permitting.[f] On August 8, 2022, FDA determined the Sponsor's July 21, 2022, July 25, 2022, and August 3, 2022 submissions constituted a major amendment.[g]

According to the Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products[h], under certain circumstances, FDA can conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness, for instance a natural history study that demonstrates a very limited median survival time or other clinically highly important outcome without treatment could represent confirmatory evidence.

2 REVIEW METHODS AND MATERIALS

DEPI reviewed the following:

- RTA 408: Post hoc propensity-matched analysis of study 408-C-1402 extension, dated August 2, 2022.

DEPI consulted the following guidances:

- Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products December 2019
- Draft Guidance for Industry: Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products[i]

3 REVIEW RESULTS

The Sponsor presented a post hoc comparative analysis of an ongoing extended access study of omaveloxolone treatment and an observational study.

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[f] NDA 216718 Mid-Cycle Communication DARRTS Reference ID: 5029547

[g] T Buracchio Review Extension – Major Amendment NDA 216718. August 8, 2022. DARRTS Reference ID: 5026626.

[h] Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, December 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products (accessed October 7, 2022)

[i] Draft Guidance for Industry: Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products, December 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug (accessed October 7, 2022)

Study 1402 extension is an ongoing, extended access study designed to provide treatment with omaveloxolone (150 mg/day) to eligible patients with FA following completion of study 1402 Part 1 or Part 2 while collecting safety and tolerability data. Data from Study 1402 Part 1 and Study 1402 Part 2 were not included in this propensity matched analysis. Only data from Study 1402 Extension were compared to natural history data.

The Clinical Outcome Measures in FA (FA-COMS) study is a global, multi-center, longitudinal, prospective observational study that has enrolled more than 1,000 patients, with follow-up as long as 19 years in some patients. Clinical outcome measures, including Friedreich's Ataxia Rating Scale (FARS) and modified Friedreich's Ataxia Rating Scale (mFARS), are assessed annually. The index date was defined as the first day of Study 1402 Extension or FA-COMS.

To assess the long-term efficacy of omaveloxolone, participants in the Study 1402 extension were propensity score matched to participants in the FA-COMS as untreated external controls. Propensity scores were based on multiple covariates: sex, baseline age, age of FA onset, baseline mFARS score, and baseline gait score. Selection of these covariates was based on clinical relevance (i.e., factors considered prognostic for FA progression) and availability in both studies. Propensity scores were estimated using logistic regression with covariates. The Sponsor noted differences in the collection of data regarding concomitant medications meant they were unable to adjust for concomitant medications. There is no approved treatment for FA. However, FA patients commonly use antioxidants, vitamins, and/or minerals, in an attempt to slow disease progression as loss of mitochondrial respiratory function and production of reactive oxygenated species are thought to contribute to FA[j]. Vitamin and mineral use were allowed in both studies and not adjusted for.

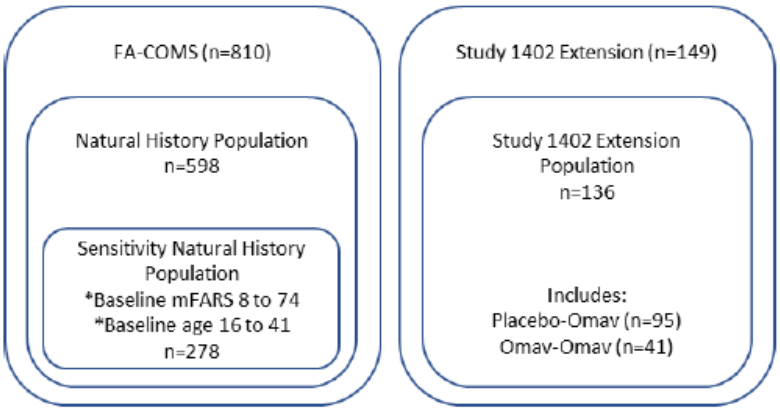
The change from baseline in mFARS at Year 3 for Study 1402 Extension patients compared to the propensity score-matched FA-COMS patients was analyzed as the primary efficacy endpoint using mixed model repeated measures (MMRM) analysis. Change from baseline in mFARS at Year 1 and Year 2 were secondary endpoints.

For inclusion in either of the study groups, patients must have had (1) baseline mFARS, (2) at least one post-baseline mFARS within 3 years after baseline, and (3) values for all propensity score model covariates (i.e., sex, age at baseline, age of FA onset, and baseline gait score). A subgroup of patients from the FA study was selected for a sensitivity analysis with the additional requirements to the FA patients (1) baseline mFARS score was within the range observed in Study 1402 Extension (mFARS 8 to 74) and (2) age at baseline was within the range observed in Study 1402 Extension (age 16 to 41 years). The study populations are presented in

[j] Myers L, Farmer JM, Wilson RB, Friedman L, Tsou A, Perlman SL, Subramony SH, Gomez CM, Ashizawa T, Wilmot GR, Mathews KD, Balcer LJ, Lynch DR. Antioxidant use in Friedreich ataxia. J Neurol Sci. 2008 Apr 15;267(1-2):174-6. doi: 10.1016/j.jns.2007.10.008. Epub 2007 Nov 7. PMID: 17988688; PMCID: PMC2279016.

Figure 1 below. The Study 1402 extension group included 136 patients and the FA-COMS population included 598 patients.

Figure 1. Study Population



Note: All study populations require at least one post-baseline mFARS within 3 years after baseline, and values for all propensity score model covariates.
*Baseline mFARS and age are within the range observed in Study 1402 Extension patients at baseline.

There were three primary analysis populations:

1. The primary pooled population included all patients in the Study 1402 extension (n=136) and their corresponding matched natural history patients (n=136).
2. The primary placebo-omaveloxolone (Placebo-Omav) population included all patients in the Study 1402 extension population who were enrolled in Study 1402 Part 1 or were randomized to placebo in Study 1402 Part and received omaveloxolone in Study 1402 Extension (n=95) and the corresponding matched natural history patients (n=95).
3. The Primary Omaveloxolone-Omaveloxolone (Omav-Omav) Population includes all patients in the Study 1402 Extension population who were randomized to receive omaveloxolone in Study 1402 Part 2 and received omaveloxolone in Study 1402 Extension (n=41) and the corresponding matched natural history patients from the natural history population (n=41).

There were also three sensitivity analysis populations in Study 1402 that corresponded with their respective analysis population, but the FA-COMS population was restricted to the sensitivity populations (n=278).

A diagram of the primary study population is presented in Appendix Figure 1. Most participants in Study 1402 were enrolled in the extension study. The mean follow-up in FA-COMS was 2.54 years (SD 0.79) and 2.60 years (SD 0.52) in the Study 1402 extension. The demographics and characteristics used to generate propensity scores were well-balanced between the groups. The demographics not included in propensity scores are presented in Appendix Table 1.

For the primary endpoint, change in mFARS at Year 3, in the Pooled Primary Population, matched FA-COMS patients progressed 6.611 mFARS points whereas patients treated with omaveloxolone in Study 1402 Extension progressed 3.004 points (difference = -3.607 points; nominal p=0.0001, Appendix Table 2). Analyses of the primary endpoint in the Primary Placebo-Omav and Primary Omav-Omav populations yielded similar results, with a slowing of progression in mFARS of >50% (Appendix Table 3) in Study 1402.

The mean change in mFARS from baseline over time is presented in Appendix Figure 2. At each year, patients in Study 1402 Extension experienced a smaller change from baseline in mFARS than the matched FA-COMS patients.

The Sponsor concluded, "although there are limitations in performing this cross-study analysis, the limitations do not render the results uninterpretable. The FA-COMS cohort identified by propensity score matching is highly comparable to the Study 1402 Extension patients for both baseline characteristics and standard of care; therefore, the observed difference in disease progression (as assessed by mFARS) can be attributed to omaveloxolone treatment."

4 DISCUSSION

In a propensity-matched analysis comparing omaveloxolone exposed participants enrolled in an extension study and participants in a natural history, omaveloxolone exposed participants experienced less progression of FA as measured by the mFARS score.

There are a few limitations to be considered:
Confounding: This study was not randomized, which limits the ability to control for measured and unmeasured confounders. The selection of covariates included in the propensity-matched analyses were based on their association with FA progression but also the collection of and completeness of covariate data in both studies. Notably, there are no approved treatments for FA, thus it is unlikely that concomitant medication use is confounding the observed results. The strongest predictors of FA progression were age (progression is fastest in younger patients) and longer guanine-adenine-adenine [GAA] repeat length).[k] In an analysis of FARS-COM participants, GAA1 repeat length was the strongest contributor after accounting for baseline FA severity.[l] GAA repeat length was not included in the propensity score as there were missing values, however the Sponsor stated that the slight differences between the two groups were not clinically meaningful. Age was included in the propensity score.

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[k] Patel M, Isaacs CJ, Seyer L, Brigatti K, Gelbard S, Strawser C, Foerster D, Shinnick J, Schadt K, Yiu EM, Delatycki MB, Perlman S, Wilmot GR, Zesiewicz T, Mathews K, Gomez CM, Yoon G, Subramony SH, Brocht A, Farmer J, Lynch DR. Progression of Friedreich ataxia: quantitative characterization over 5 years. Ann Clin Transl Neurol. 2016 Jul 25;3(9):684-94. doi: 10.1002/acn3.332. PMID: 27648458; PMCID: PMC5018581

[l] Ibid

Selection bias: Study 1402 extension patients may have been healthier at baseline or responded better to omaveloxolone than those who did not participate in the extension study, which would bias measures of association towards a beneficial effect of omaveloxolone. However, the study included a sensitivity analyses of Study 1402 participants who had not taken omaveloxolone, which also reported a beneficial association[m]. Another concern is that the natural history study has less stringent inclusion and exclusion criteria, thus patients in the natural history study may be more likely to have severe FA, which would bias associations away from the null. The Sponsor conducted sensitivity analyses with the additional requirements of having the same age and baseline mFARS score as the Study 1402 extension and the results still supported a beneficial effect of omaveloxolone. However, even in this sensitivity analysis the FA-COMS cohort did not have the same inclusion/exclusion criteria as the extension study because extension study participants were excluded if they had any of the following:

1. History of clinically significant left-sided heart disease and/or clinically significant cardiac disease
2. Uncontrolled diabetes (HbA1c >11.0%)
3. B-type natriuretic peptide value >200 pg/mL
4. Cognitive impairment that may preclude ability to comply with study procedures

Thus, participants in the extension study were likely still healthier and more able to comply with study procedures (i.e., completion of mFARS assessment) than the FA-COMS participants, which would bias associations away from the null and towards a beneficial effect of omaveloxolone.

Loss to follow-up: Another concern is that participants in the extension study were required to complete phase 1 or 2 of Study 1402 and 3 years of follow-up. The index date for the extension study was after participants completed phase 1 or 2 of Study 1402, while the index date for FA-COMS was the first day of study enrollment. For Study 1402 Part1 patients, this resulted in a minimum 21-month off-treatment period prior to enrolling in Study1402 extension. A potential limitation of this analysis is that participants enrolled in FA-COMS did not have to complete an initial phase of the study in the same way that participants in the extension study did, which could lead to healthier participants in the extension study and biasing the measures of association towards a beneficial effect for omaveloxolone (immortal time bias). However, most Study 1402 participants did enroll in the extension study (appendix figure 1), suggesting that this is not a major limitation. There was also loss to follow-up during the extension study. Subjects who do not respond omaveloxolone would be more likely to stop participating in the extension study,

[m] In the Primary Placebo-OmavPopulation, in which Study 1402 Extension patients were considered treatment-naïve at Extension baseline, progression in mFARS was slowed by 56% in Study 1402 Extension patients. Page 31 of Sponsor's submission.

which would bias measures of association away from the null. However, the year 1 and 2 analyses also indicated that omaveloxolone was effective.

Use of external controls: Study participants and researchers were not blinded to treatment status and the data collection processes differed between the two studies. Thus, there could be differences in the way study staff measured or recorded outcomes that biased the study effect estimates. This type of bias is unpredictable, researchers may be more motivated to see a lack of progression in treated patients or there could be differences in methods that bias towards the null. The main outcome (mFARS) is a clinician-observed/performance-based outcome with standardized instructions. The Sponsor notes that the same investigator served as the primary trainer for the mFARS assessment to all Study 1402 Extension investigators and FA-COMS investigators and there was overlap between study sites. However, these investigators were not blinded to treatment, thus misclassification is still a concern.

Post-hoc analysis: This study was conducted post hoc after DN1 communicated concerns regarding the evidence provided in the original assessment. This does not adhere to the FDA's draft guidance for industry regarding use of real-world data requirements for transparency regarding data collection and analysis.[n] FDA must be confident that data sources were not selected, or specific analyses were not conducted to favor a certain conclusion. To adhere to this requirement, the Sponsor should provide evidence that the protocol and SAP were finalized prior to reviewing the outcome of a study and before performing pre-specified analyses. The Sponsor did not provide a statistical analysis plan or protocol before submitting the results of this study and the statistical analysis plan provided with the study results is dated July 20, 2022, less than two weeks before the final report. It is not specified if other data sources or statistical models were considered or if any additional analyses were conducted, which limits the amount of confidence DEPI can have that these methods were not selected to provide support for the efficacy of omaveloxolone. For instance, without a pre-specified analysis plan, the Sponsor may have conducted exploratory analyses when selecting statistical models and strategies to adjust for confounding and reported only the results that provide evidence of efficacy omaveloxolone.

5 CONCLUSION

Overall, the comparative analysis presented by the Sponsor has limitations expected in a study using an external control group (e.g., uncontrolled confounding, selection bias, loss to follow-up). The analysis was conducted post hoc and did not follow the FDA's guidelines for using real-world data. However, this study did have the

[n] Draft Guidance for Industry: Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products, December 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug (accessed October 7, 2022)

strengths of individual-level data which allowed for propensity matching and adjustment for age (one of the strongest predictors of FA progression).

APPENDICES

Figure 1. CONSORT Diagram of the Study Population

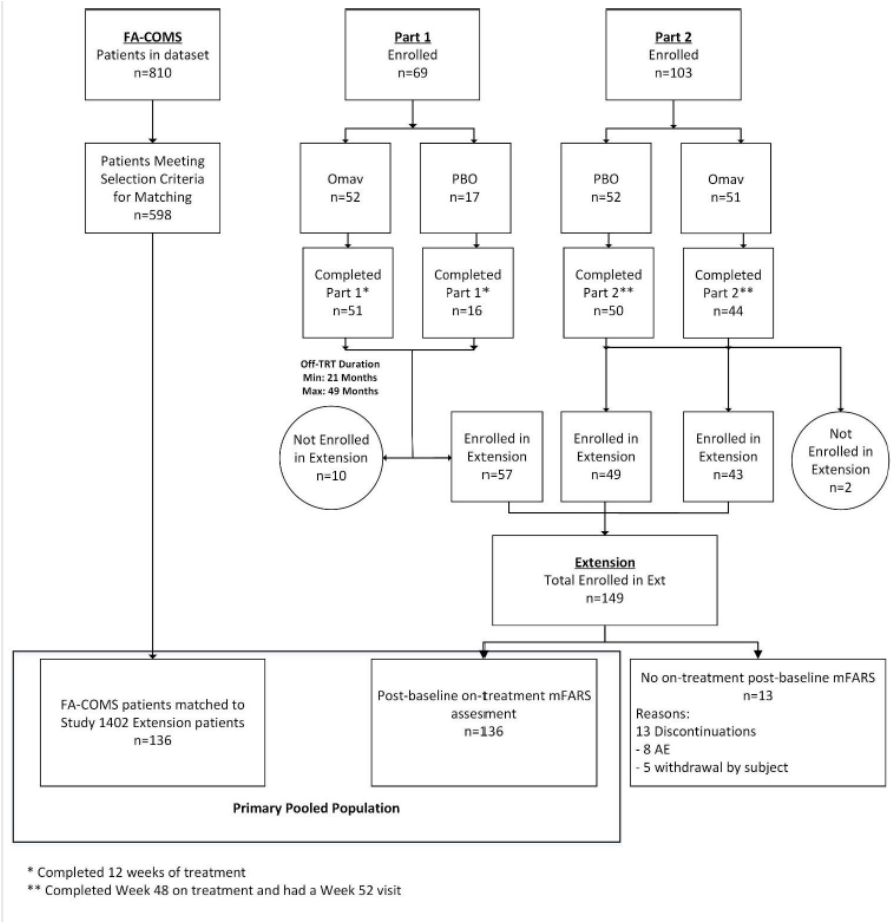
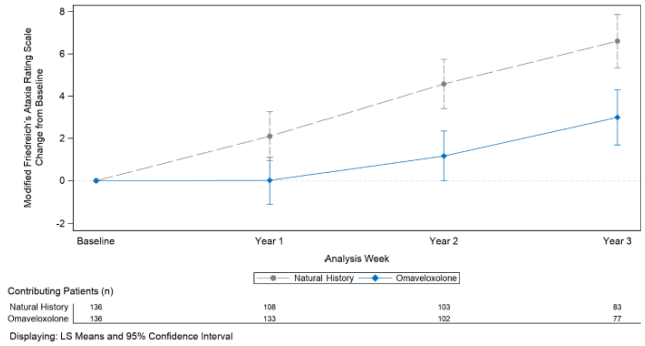


Figure 2. LS Mean Change from Baseline in mFARS Over Time (Primary Pooled Population). Source Figure 6 in Sponsor's submission



Note: Natural History (NH) = Matched FA-COMS
Source: Figure 14.2.1.1

Table 1. Other Demographics and Baseline Characteristics (Primary Pooled Population). Source Table 7 in the Sponsor's report.

Characteristic	Statistic	Matched FA-COMS	Study 1402 Extension
Ethnicity (n [%])	n	136	136
	Hispanic or Latino	6 (4.4%)	6 (4.4%)
	Not Hispanic or Latino	129 (94.9%)	130 (95.6%)
	Not reported	1 (0.7%)	0
Race (n [%])	n	130	136
	White	125 (96.2%)	133 (97.8%)
	Non-White	5 (3.8%)	3 (2.2%)
Height (cm)	n	89	136
	Mean (SD)	165.101 (14.6676)	169.305 (10.4216)
Weight (kg)	n	95	136
	Mean (SD)	60.952 (20.6625)	69.084 (16.7309)
BMI (kg/m^2)	n	89	136
	Mean (SD)	22.007 (5.6779)	24.019 (5.2279)
Systolic Blood Pressure (mmHg)	n	82	136
	Mean (SD)	121.4 (15.00)	121.1 (13.54)
Diastolic Blood Pressure (mmHg)	n	82	136
	Mean (SD)	73.2 (10.53)	75.3 (8.65)
Heart Rate (beats/min)	n	82	136
	Mean (SD)	85.2 (15.40)	79.8 (12.58)
ADL Total Score	n	124	136
	Mean (SD)	11.78 (5.937)	12.51 (4.947)

Characteristic	Statistic	Matched FA-COMS	Study 1402 Extension
GAA1 Repeat Length	n	129	119
	Mean (SD)	589.7 (245.50)	720.9 (269.58)
	≥ 675, n (%)	54 (41.9%)	66 (55.5%)
GAA2 Repeat Length	n	121	116
	Mean (SD)	862.8 (232.38)	727.6 (296.93)

Abbreviations: ADL=Activities of Daily Living; BMI=body mass index; FA=Friedreich's ataxia; FARS=Friedreich's ataxia rating scale; mFARS=modified Friedreich's ataxia rating scale
Note: Only patients with available information are summarized for each parameter. Additional baseline characteristics are provided in Table 14.1.2.1.
Source: Table 14.1.1.1 and Table 14.1.2.1

Table 2. Change in mFARS Score at Year 3 (Primary Pooled Population). Source: Table 9 in the Sponsor's submission.

	Pooled (Match 1)	
	Matched FA-COMS (N=136)	**Study 1402 Extension** (N=136)
Baseline, Mean (±SD)	41.030 (16.1017)	42.223 (12.6019)
mFARS Change from Baseline (LS Mean [±SE])		
Year 3	6.611 (0.6459)	3.004 (0.6638)
Year 3 Difference[a]	-	-3.607 (0.9263) p= 0.0001

Abbreviations: LS=least squares; mFARS=modified Friedreich's ataxia rating scale
[a] Difference is Study 1402 Extension – matched FA-COMS.
Source: Table 14.2.1.1 and Table 14.2.2.1

Table 3. Change in mFARS Score at Year 3 (Primary Placebo-Omav and Primary Omav-Omav Populations). Source Table 10 in the Sponsor's submission.

	Placebo-Omav (Match 2)		Omav-Omav (Match 3)	
	Matched FA-COMS (N=95)	**Study 1402 Extension** (N=95)	**Matched FA-COMS** (N=41)	**Study 1402 Extension** (N=41)
Baseline, Mean (±SD)	44.539 (18.0399)	42.814 (12.7937)	39.639 (16.7957)	40.854 (12.1891)
mFARS Change from Baseline (LS Mean [±SE])				
Year 3	7.293 (0.7194)	3.206 (0.7586)	6.141 (1.241)	2.377 (1.3263)
Year 3 Difference[a]	-	-4.087 (1.0453) p=0.0001	-	-3.764 (1.8173) p=0.0400

Abbreviations: LS=least squares; mFARS=modified Friedreich's ataxia rating scale
[a] Difference is Study 1402 Extension – matched FA-COMS.
Note: Each population (Placebo-Omav, Omav-Omav) represents a different set of matched patients.
Source: Table 14.2.1.2, Table 14.2.1.3, Table 14.2.2.2, and Table 14.2.2.3

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/s/

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	February 23, 2023
Reviewer:	Catherine Callahan, PhD, MA Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
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Subject:	ARIA sufficiency memo for study of safety of omaveloxolone exposure during pregnancy and lactation.
Drug Name:	Omaveloxolone (SKYCLARYS)
Application Type/Number:	NDA 216718
Applicant/sponsor:	Reata Pharmaceuticals, Inc.
OSE RCM #:	2022-2856

1. BACKGROUND INFORMATION

1.1. Medical Product

Omaveloxolone is currently under review by the Division of Neurology 1 (DN1) for the proposed indication of Friedreich's ataxia (FA). FA is an ultra-rare, genetic, rapidly progressive neurodegenerative disorder that affects approximately 5,000 patients in the United States and 22,000 patients globally. There are currently no FDA-approved therapies for FA.[1]

Omaveloxolone (also known as RTA 408) is a novel, orally bioavailable, semi-synthetic oleanane triterpenoid compound that activates the transcription factor nuclear factor, erythroid 2 like 2 (Nrf2), which regulates the response to cellular oxidative stress and coordinates the expression of genes that normalize mitochondrial function, restore redox balance, and reduce inflammation.[2] The recommended dosage is 150mg (as three 50mg capsules) once daily. The draft label for omaveloxolone has warnings and precautions for elevations of aminotransferases and B-type natriuretic peptide, lipid abnormalities, and decreased body weight. The most common adverse reactions were aminotransferase increase, nausea, diarrhea, and oropharyngeal pain.[3]

1.2. Describe the Safety Concern

DN1 requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for a broad-based signal detection study of omaveloxolone exposure during pregnancy and lactation. Age of FA onset is variable but typically occurs during childhood or adolescence,[4] thus omaveloxolone use during pregnancy is possible. In a retrospective case series, there was no association between FA and abortion, preterm birth, or preeclampsia.[5] Omaveloxolone may also reduce the effectiveness of hormonal contraceptives. The draft label includes recommendations to advise patients to avoid concomitant use with hormonal contraceptives and use an alternative contraceptive method (e.g., non-hormonal intrauterine system) or additional non-hormonal contraceptive (e.g., condoms) during concomitant use and 28 days after omaveloxolone exposure.[6]

Pregnancy and breastfeeding were criteria for discontinuation in all omaveloxolone

[1] NDA 216718 Reviewer's guide
[2] Ibid
[3] SKYCLARYS™ (omaveloxolone) draft label as of February 23, 2023.
[4] Friedreich Ataxia Fact Sheet https://www.ninds.nih.gov/friedreich-ataxia-fact-sheet#:~:text=Symptoms%20typically%20begin%20between%20the,have%20onset%20after%20age%2025. (accessed December 29, 2022)
[5] L Friedman, et.al, Pregnancy with Friedreich ataxia: a retrospective review of medical risks and psychosocial implications, American Journal of Obstetrics and Gynecology, Volume 203, Issue 3, 2010
[6] SKYCLARYS™ (omaveloxolone) draft label as of February 23, 2023.

studies. There were no pregnancies exposed to omaveloxolone in the Reata safety database. [7]

The proposed labeling for omaveloxolone has the following information regarding pregnancy:[8]

> 8.1 Pregnancy
> Risk Summary
> There are no adequate data on the developmental risks associated with the use of SKYCLARYS in pregnant women. In animal studies, (b) (4) In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.
>
> Data
> Animal Data
> (b) (4)
>
> 8.2 Lactation
> Risk Summary
>
> There are no data on the presence of omaveloxolone in human milk. The effects on milk production and the breastfed infant are unknown. Omaveloxolone (b) (4) in the milk of lactating rats following (b) (4). 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 (b) (4) from SKYCLARYS or the underlying maternal condition [see Data].
>
> (b) (4)

[7] Reata, Omaveloxolone Summary of Clinical Safety. As of August 17, 2021.
[8] Omaveloxolone Prescribing Information as of February 23, 2023

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† *If checked, please complete General ARIA Sufficiency Template.*

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☐ Electronic database study without chart review

☒ Other, please specify: Descriptive pregnancy safety study, which enrolls exposed pregnancies into a protocol-driven observational cohort study for descriptive analyses and collects follow-up data, including detailed case narratives. These studies do not have the sample size required for inferential analyses. A single-arm pregnancy safety study is appropriate because this drug is indicated for an ultra-rare disease.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population: ARIA lacks the capacity to identify lactating women.

Outcomes: ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.

Covariates: ARIA does not have detailed information on potential confounders. The descriptive pregnancy safety study being considered would collect detailed narratives with information on potential covariates, such as lifestyle factors and prenatal supplement use.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully tested and implemented in postmarketing surveillance of maternal and fetal outcomes. The ARIA analytic tools that assess drug use in pregnancy (and maternal and neonatal outcomes) currently include only women with a live-birth delivery.

2.5. Please include the proposed PMR language in the approval letter.

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to omaveloxolone during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

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/s/

CATHERINE L CALLAHAN
02/23/2023 09:19:41 AM

KIRA N LEISHEAR WHITE
02/23/2023 09:20:44 AM

SUKHMINDER K SANDHU
02/23/2023 09:30:24 AM

JUDITH W ZANDER
02/23/2023 09:30:58 AM

PATRICIA L BRIGHT
02/23/2023 09:33:14 AM

GERALD J DALPAN on behalf of ROBERT BALL
02/24/2023 12:27:25 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 21, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216718
Product Name and Strength:	Skyclarys (omaveloxolone) capsule, 50 mg
Applicant/Sponsor Name:	Reata Pharmaceuticals, Inc.
OSE RCM #:	2022-304-1
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on February 17, 2023 for Skyclarys. The Division of Neurology 1 (DN 1) requested that we review the revised container label for Skyclarys (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a], and via email communication with the Applicant after subsequent discussion with the Division regarding appropriate administration of the capsule (i.e., Swallow whole. Do not open, crush, or chew.).

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Morris, C. Label and Labeling Review for Skyclarys (NDA 216718). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 JUL 29. RCM No.: 2022-304.

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JOHN C MORRIS
02/21/2023 01:37:44 PM

STEPHANIE L DEGRAW
02/21/2023 03:16:45 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 14, 2023

To: Brenda Reggettz, PharmD, Senior Regulatory Project Manager, Division of Neurology Products I (DN1)

Veneeta Tandon, M.D., Clinical Reviewer, (DN1)

Tracy Peters, Pharm D, Associate Director for Labeling, (DN1)

From: Adesola Adejuwon, Pharm D, MBA, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for SKYCLARYS™ (omaveloxolone) capsules, for oral use

NDA: 216718

Background:
In response to DN1's consult request dated May 4, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI) and carton and container labeling for the original NDA submission for SKYCLARYS™ (omaveloxolone) capsules, for oral use (Skyclarys).

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 30, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on February 7, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on February 6, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at 240 402 5773 or Adesola.Adejuwon@fda.hhs.gov.

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/s/

ADESOLA F ADEJUWON
02/14/2023 09:53:35 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 7, 2023
To:	Brenda Reggettz, PharmD Regulatory Project Manager, RPM **Division of Neurology 1 (DN1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adesola Adejuwon, Pharm D, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	SKYCLARYS (omaveloxolone)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 216718
Applicant:	Reata Pharmaceuticals, Inc.

1 INTRODUCTION

On January 28, 2022, Reata Pharmaceuticals, Inc. submitted for the Agency's review Part 1 of 2 Presubmission to a rolling submission of an original New Drug Application (NDA) 216718 for SKYCLARYS (omaveloxolone) capsules, for oral use. In addition, Reata Pharmaceuticals submitted a request for priority review, request for proprietary name review, request for rare pediatric disease priority review voucher, and request for PDUFA fee exemption. Omaveloxolone is a new molecular entity (NME), for the treatment of Friedreich's ataxia. The NDA was submitted under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C). Omaaveloxolone was granted orphan drug status designation by the FDA in June 2017.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology 1 (DN1) on May 4, 2022 for DMPP and OPDP to review the Applicant's proposed PPI for SKYCLARYS (omaveloxolone) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft SKYCLARYS (omaveloxolone) PPI received on January 28, 2022 and received by DMPP and OPDP on January 30, 2023.
- Draft SKYCLARYS (omaveloxone) Prescribing Information (PI) received on January 28, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 30, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additonally, in 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy PPI and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
02/07/2023 09:33:44 AM

ADESOLA F ADEJUWON
02/07/2023 10:52:59 AM

LASHAWN M GRIFFITHS
02/07/2023 11:08:38 AM

Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	216718
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	omaveloxolone
Indication	Frederick's Ataxia
Applicant	Reata Pharmaceuticals, Inc.
Requesting Division	Division of Neurology 1
Primary Reviewer	Ling Lan, MD, PhD, Clinical Analysist, DILI Team, DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Other Reviewers	Edwige Chiogo Vouffo, PharmD, PhD, OND/DHN
Signatory Authority	Frank A. Anania, MD Acting Director, OND/DHN
Assessment Date	Dec 5, 2022

Context: Omaveloxolone (OMX) is an oral small molecule that activates nuclear factor erythroid 2-related factor 2 (Nrf2) by binding the Kelch-like ECH-associated protein 1 (Keap1). This indication for OMX is Frederick's Ataxia (FA). Nrf2 activates numerous genes including those that are anti-oxidative and promote glutathione synthesis. Impaired Nrf2 function is central to FA pathophysiology, hence the rationale for developing the investigational product (IP). A higher percentage of subjects on OMX had transaminase elevations compared to subjects in the placebo arm. This raised concerns for DN1 that drug-induced liver injury (DILI) was occurring. DN1 requested consultation from the DILI Team's for comments and advice for proposed labeling and the need for a post marketing requirement.

Executive Summary: DHN concludes that evidence for a strong DILI signal is not evident and liver injury risk should not hold up approval. There were no subjects with jaundice, and thus no Hy's Law or significant cholestatic injury cases. The enzyme elevations may be due to off-target gene expression of ALT and AST or modest DILI. The aminotransferase elevation pattern in most subjects resembles profiles seen with another Nrf2 activator, bardoxalone. In that NDA, the DILI team concluded that increased gene expression was a plausible competing cause for aminotransferase elevations, and such elevations tended to decline with continued exposure to drug. We have a similar conclusion with OMX with benign gene expression and modest DILI with adaption being the leading explanations for the enzyme elevations. We cannot entirely rule out increased risk for a clinically significant or serious form of DILI that may appear in a larger post-market population because the number of subjects in the OMX trials

was small. Labeling should include description of the incidence and pattern of liver enzyme elevation. Baseline liver enzymes and total bilirubin should be checked, and early monitoring should be considered. Post market studies assessing for liver injury on OMX also should be considered. Full, detailed recommendations are in Section 5 below.

Consultation Sections:

Section 1.0 – Target Disease and Rationale
Section 2.0 - ADME pertinent to DILI
Section 3.0 - Non-clinical data pertinent to DILI.
Section 4.0 - Clinical data
Section 5.0 – Assessment & Recommendations.
Appendix A: Effect of OMX on Aminotransferase mRNA
Appendix B: Study 408-C-1402 Part 1 and Part 2 schema
Appendix C: Updated subject enrollment and retainment in Extension study

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Abbreviations:
AP or ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BMI: body mass index
CK: creatinine phosphokinase
CYP: cytochrome P450
DB: direct bilirubin
DILI: drug-induced liver injury
FA: Frederick's Ataxia
FXN: frataxin
GGT: gamma-glutamyl transferase
HDS: herbal and dietary supplements
HFE: Human homeostatic iron regulator gene
IP: investigational product
Keap1: Kelch-like ECH-associated protein 1
Nrf2: nuclear factor, erythroid 2-like 2
OMX: omaveloxolone
R-value: ALT/ULN ÷ ALP/ULN
RTA-408: omaveloxolone
TB: total bilirubin
US: ultrasound
ULN: upper limit of normal

1.0 Target Disease and Rational

1.1 Target Disease: Frederick's ataxia (FA) is genetic disorder leading to uncoordinated motor function due to cerebellar dysfunction. Most patients have loss of function mutations in the frataxin (FXN) gene that codes for its namesake mitochondrial protein,

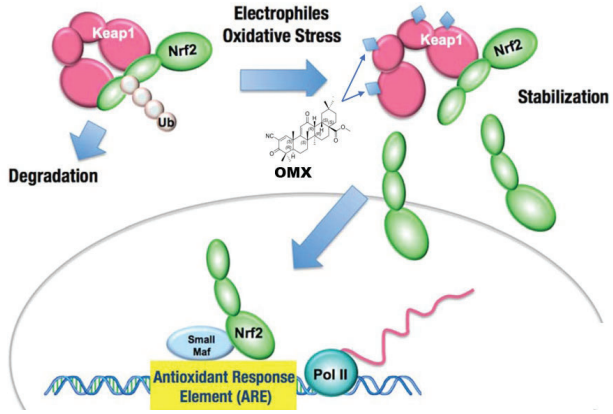
frataxin.[1] The FXN protein is essential for iron homeostasis (e.g., iron chaperoning, iron detoxification). Malfunctioning FXN leads to oxidative stress and iron accumulation in the mitochondria. These abnormalities lead to atrophy of the efferent neurons in the cerebellum. The mitochondrial iron loading does not manifest as chronic liver disease (i.e., hemochromatosis), and there are no strong links between the human homeostatic iron regulator (HFE) gene mutations, FA or FXN mutations.

While FA is the most common hereditary ataxia accounting for up half of all cases, it is rare overall with a prevalence of 1 in 30,000 to 50,000 whites. The prevalence in Asia and sub-Saharan Africa is far lower. Age of onset is usually less than 25 years, and the disease is progressive. Besides the ataxia, the primary manifestations include cardiomyopathy and diabetes mellitus. Quality of life and longevity are significantly impaired. The ataxia involves all four limbs. The mean time to wheelchair use is 11 to 25 years. Hearing loss, dysarthria, and dysphagia are also common. There may be mild cognitive dysfunction. Cardiomyopathy is usually hypertrophic, and heart failure is a frequent cause of death. Most patients live only into their fourth or fifth decade.

There are no approved treatments for FA. The iron chelator, deferiprone, has not been effective and antioxidants have had limited success for treatment of FA.

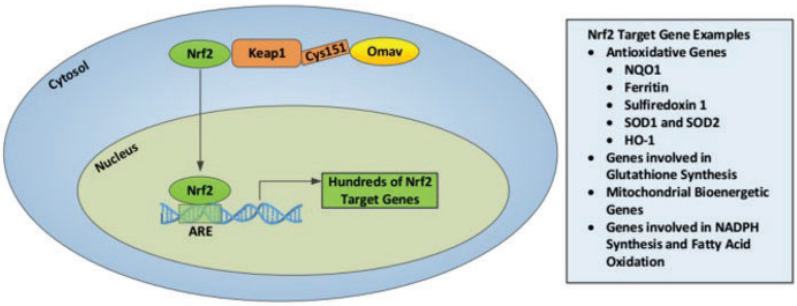
1.2 Rationale: Impaired Nrf2 signaling is considered critical to FA pathophysiology. OMX is an oral small molecule that binds Kelch-like ECH-associated protein 1 (Keap1). Keap1 is a negative regulator of Nrf2 (**Figure 1**); hence, Keap1 binding results in activation of Nrf2 which leads to transcription of key genes associated with antioxidant defense, the anti-inflammatory response, and cytoprotection (**Figure 2**), thereby reducing cerebellar damage of FA.

Figure 1: OMX activation of Nrf2 via Keap1 binding[2]



[1] UpToDate https://www.uptodate.com/contents/friedreich-ataxia?search=Frederick%27s%20ataxia&source=search_result&selectedTitle=1~32&usage_type=default&display_rank=1#H613240487 (last updated Aug 19, 2022)
[2] Adapted from Mitsuishi Y, et al. The Keap1–Nrf2 system in cancers: stress response and anabolic metabolism, Front Oncology, 2012, 2:1-13, https://doi.org/10.3389/fonc.2012.00200

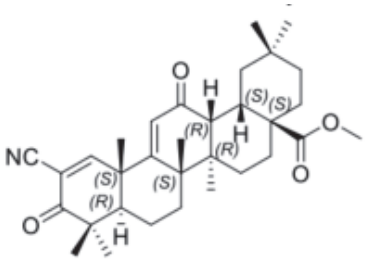
Figure 2: Examples of downstream target gene expressed by Nrf2 activation[3]



2.0 ADME data

2.1 Omaveloxolone (OMX) structure (**Figure 3**):

Figure 3: Skeletal chemical structure of OMX[4]



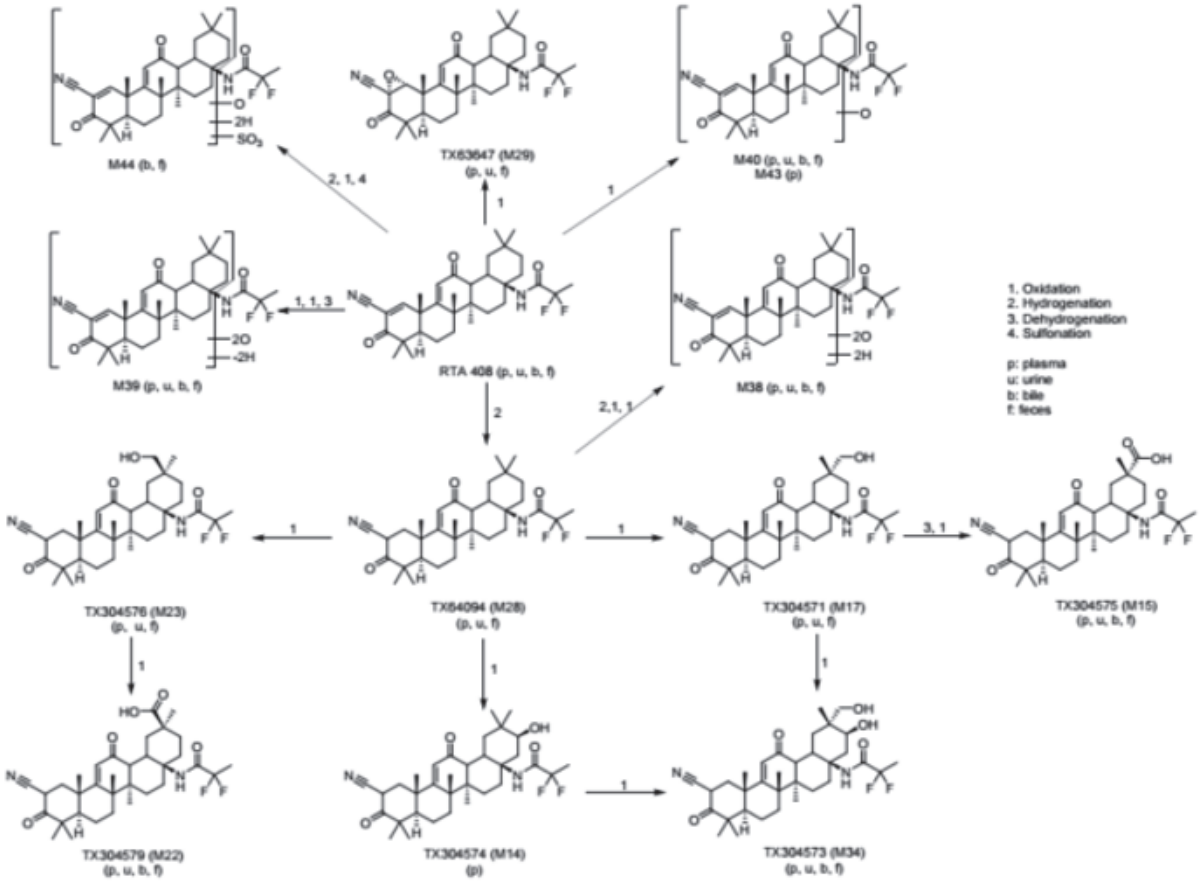
2.2 Absorption: OMX is rapidly absorbed in rats. After an oral dose, OMX was rapidly absorbed and quantifiable within eight hours in rats. Oral administration of OMX had a T_{max} of one hour. Oral bioavailability was 48.6%. However, a single oral OMX demonstrated slower absorption in monkeys. The median T_{max} was eight hours and the mean C_{max} and $AUC_{0\text{-}24hr}$ were reported to be 3.57 and 65 hr*ng/mL, respectively. Bioavailability of OMX was low at 3.41% following oral administration which the applicant attributes to slow absorption and extensive metabolism.

2.3 Distribution: In plasma protein binding studies, OMX was highly protein bound in mice (92.7%), rats (94.7%), rabbits (96.0%), dogs (95.2%), minipigs (99.6%), monkeys (94.8%), and humans (96.9%). There was minimal tissue binding, so a low volume of distribution is expected.

2.4 Metabolism: Following oral and IV doses in male monkeys [^{14}C] labelled OMX underwent extensive metabolism, primarily by reduction after IV administration and oxidation and reduction after oral administration. A single oral dose in monkeys yielded 24 quantifiable metabolites. **Figure 4** shows just 12 of these metabolites. A seven-day pharmacokinetic study in humans showed TX304579 and TX304571 to be the primary metabolites in plasma. In a 14-day toxicity in rats, the NOAEL was 30 mg/kg/day; and in a 28-day toxicity in rats, the NOAEL was estimated to be 3 mg/kg/day.

[3] NDA215484 (215484 - 0007 - (7) - 2021-03-25 - ORIG-1 /Clinical/Response To Information Request) - Nonclinical Overview (#13)
[4] NDA215484 (215484 - 0007 - (7) - 2021-03-25 - ORIG-1 /Clinical/Response To Information Request) - General Information (#2)

Figure 4: Proposed biotransformation pathways of OMX in monkeys[5]



2.5 Elimination: The half-life for orally administration of OMX in mice and rats varied from 5.36 to 11.2 hours following oral daily administration of 10, 30, or 100 mg/kg/day of OMX. [^{14}C] OMX was eliminated almost exclusively by the fecal route as metabolites following either oral or IV administration in monkeys. IV administration resulted in 70% fecal excretion, with a high concentration of radioactivity in the gallbladder. Only 5% was found in the urine.

3.0 Non-clinical data

3.1 In vitro data

Transporter inhibition: Following in vitro studies, OMX showed little to no inhibitory activities against BCRP, BSEP, OAT3, OATP1B1, and OCT2 systemic transporters. OMX inhibited MDR1 and OCT1 systemic transporters as well as renal transporters OAT1. We did not find data on MRP2 inhibition.

CYP metabolism: Human microsome studies suggest CYP3A4 is the major CYP involved in OMX metabolism with CY2C8 and CYP2J2 having minor roles. OMX showed direct inhibition activity on CYP2C9, and CYP3A4/5 with IC_{50} of 4.8 and 4.9 μM

[5] NDA216718 (216718 - 0019 - (18) - 2022-07-26 - ORIG-1 /Quality/Response To Information Request) - Study RTA-P-18011 (#382)

respectively. There was no evidence of time-dependent inhibition except for CYP1A2 at the highest concentration tested (10 μM).

Glutathione effects: There was an increase in glutathione levels in rats consistent with an off-target effects of OMX on glutathione gene expression. However, we did not find glutathione trapping data.

Mitochondrial effects: OMX improved mitochondrial function based on ATP-linked, basal, and maximal respiration, spare respiratory capacity, and non-mitochondrial respiration oxygen consumption rates in C2C12 cells assessed using Seahorse mitochondrial stress tests.

ALT and AST mRNA studies: These studies are particularly pertinent to this NDA because the applicant suggests off-target OMX expression of transaminase mRNAs may explain the ALT and AST elevations seen in the clinical trials. This explanation was also proposed in NDA 215484 using bardoxolone, another Nrf2 activator with the same mechanism of action as OMX.[6] The DILI Team concluded that the increased ALT and AST mRNA was the most likely reason for transaminase elevation patterns observed in NDA 215484, but could not rule out a DILI event with adaptation.[7] For OMX, the applicant did two cell culture studies examining transaminase mRNA levels.

Study RNA400-R-1120 used a hepatocyte cell-line from murine mouse livers (AML-12 cells) which suggested that OMX increases mRNA levels for isozymes ALT1 and AST1 while mRNA levels for ALT2 and AST2 declined (**Table 2**).[8] Cells were incubated with OMX at two concentrations, RNA was isolated and copy DNA (cDNA) created by reverse transcription. The study used primers for ALT1, ALT2, AST1, and AST2 mRNA for quantitative PCR. While ALT1 and AST1 segregate to the cytoplasm and ALT2 and AST2 to mitochondria, serum levels of all four rise in liver injury.[9],[10] Thus, both isozymes 1 and 2 contribute to the ALT and AST elevations in clinical liver injury.

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[6] Lewis JH, et al. Effects of Bardoxolone Methyl on Hepatic Enzymes in Patients with Type 2 Diabetes Mellitus and Stage 4 CKD. *Clin Tranl Sci*. 2021; 0:1-11, doi:10.1111/cts.12868

[7] (DARRT session needs to be opened first for link to work) https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80616726

[8] NDA216718 (216718 - 0035 - (35) - 2022-10-26 - ORIG-1 /Clinical/Response To Information Request) - RTA400-R-1120

[9] Yan RZ, et al. Alanine Aminotransferase Isoenzymes: Molecular Cloning and Quantitative Analysis of Tissue Expression in Rats and Serum Elevation in Liver Toxicity. *Hepatology.* 200; 49:598-607.

[10] Nishimura T, et al. Blood Level of Mitochondria1 Aspartate Aminotransferase as an Indicator of the Extent of Ischemic Necrosis of the Rat Liver. *Hepatology*. 1986; 6:701-7.

Table 2: Relative fold mRNA changes for ALT and AST isozymes after OMX (RTA408). incubation. Gpt1 = ALT1, Gpt2 = ALT2, Got1 = AST1, Got2 = AST2[11]

		RTA 408 (nM)		
Gene Symbol	**Alternate Gene Symbol**	**0**	**250**	**500**
Nqo1	N/A	0.99 ± 0.33	38.28 ± 2.74	20.66 ± 1.73
Gpt1	*Alt1*	1.00 ± 0.15	1.89 ± 0.17	2.64 ± 0.27
Gpt2	*Alt2*	0.81 ± 0.10	0.69 ± 0.12	0.66 ± 0.11
Got1	*Ast1*	0.89 ± 0.06	0.93 ± 0.08	1.36 ± 0.09
Got2	*Ast2*	1.05 ± 0.06	0.74 ± 0.07	0.60 ± 0.05

* In each experiment, values for each gene were normalized to one of the three replicates of its respective DMSO control. Values in the table are the average ± SEM of three independent experiments.

Study RTA400-R-2002 used similar methods but in four different cell types (mouse macrophages, mouse myoblasts, human colorectal adenocarcinoma cells, and rat proximal tubule cells). OMX increased mRNA for ALT1 or ALT2, or both, in all four cell lines. Only the colon cancer cell line had increased AST1 mRNA with OMX exposure and only at higher concentrations. All other experiments showed declines or no change in AST1 and AST2 mRNA levels. Data from the mouse macrophage experiments are shown in **Appendix A**. While increases in mRNA are statistically significant, it is unclear how much these changes translate to expression for serum aminotransferases in human subjects. The fold-changes are markedly smaller compared to the on-target positive control gene, Nqo1 (**Appendix A**, bar graph E). Moreover, both studies used concentrations 8 to 120-fold higher than what the Cmax expected in serum based on a molecular weight of 0.55 kilodaltons[12] (3.74 ng/ml versus 32 to 454 ng/ml).

3.2 Animal data: Overall, increased liver weights and liver enzyme elevations were seen in monkeys and rats exposed to OMX, but at necropsy no significant necrosis or inflammation in the liver was observed. The most significant liver histologic finding was biliary hypertrophy and hyperplasia without cholestasis.

3.3 Summary of ADME and toxicology data: Although OMX is extensively metabolized by the liver, non-clinical data do not suggest a high risk for DILI and suggest the possibility of benign increase ALT and AST mRNA expression (**Tables 3 and 4**).

[11] NDA216718 (216718 - 0035 - (35) - 2022-10-26 - ORIG-1 /Clinical/Response To Information Request) - RTA400-R-1120 (#14)
[12] NDA216718 (216718 - 0012 - (12) - 2022-06-21 - ORIG-1 /Quality/Response To Information Request) - Nonclinical Overview (#8)

Table 3: Summary of ADME data pertinent to DILI[13]

Item	Finding
Absorption	Rapid in rodents; slow in monkeys with low bioavailability
Distribution	OMX is highly protein bound with low volume of distribution.
Metabolism	Multiple (>20) metabolites in monkey studies. NOAEL was 30 mg/kg/day in a 2-week toxicity and 3 mg/kg/day in a 28-day study.
Elimination	Fecal and biliary of mainly metabolites; minimal renal excretion

Table 4: Toxicology summary table[14]

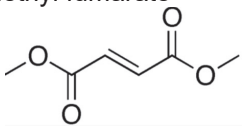
Item	Finding
In vitro studies	
Major CYPs	CYP3A4
Reaction metabolites (i.e., glutathione trapping)	No glutathione trapping studies found
Mitochondria studies/inhibition	OMX improved mitochondrial function using seahorse stress test in C2C12 myoblast cells.
Transporter (BSEP or MRP2 inhibition)	Little to no inhibition activities on BSEP; no MRP2 data
ALT and AST mRNA studies	OMX increased ALT and AST gene expression
Animal studies	
Elevation in liver analytes (e.g., ALT, AP, TB)	Increase in transaminase observed in rats without histopathologic correlate
Liver histopathology findings (animal species)	Increased liver weight, hepatocellular hypertrophy, vacuolation, bile ductule hypertrophy noted in rats. Minimal scattered necrosis occurred.

4.0 Clinical data:

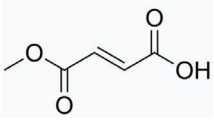
4.1 In class or near class data: Dimethyl fumarate, monomethyl fumarate, and diroximel fumarate are approved for multiple sclerosis. Their mechanism of action is not entirely clear, but they are thought to modify cysteine residues on KEAP thereby activating Nrf2. The mechanism of action (MOA) for these three compounds resembles the OMX MOA, but the chemical structures are quite different from OMX (**Figure 5**).

Figure 5: Approved Nrf2 activators' chemical structures:

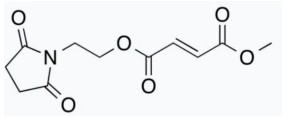
dimethyl fumarate[15]



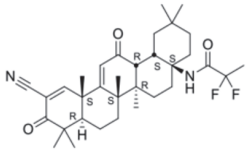
monomethyl fumarate[16]



diroximel fumarate[17]



omaveloxolone[18]



[13] Table produced by DILI Team
[14] Table produced by DILI Team.
[15] https://en.wikipedia.org/wiki/Dimethyl_fumarate
[16] https://en.wikipedia.org/wiki/Monomethyl_fumarate
[17] https://en.wikipedia.org/wiki/Dimethyl_fumarate
[18] NDA215484 (215484 - 0007 - (7) - 2021-03-25 - ORIG-1 /Clinical/Response To Information Request) - General Information (#2)

Liver toxicity is not mentioned in the dimethyl fumarate label, but it is listed under the Warnings and Precautions section for monomethyl and diroximel fumarate. The liver injury labeling is based on post-market reports of hepatocellular DILI, some of which had jaundice. No patients progressed to liver failure, death, or transplant. Labels for monomethyl fumarate and diroxemel fumarate suggest baseline liver enzyme and TB be checked with monitoring as clinically indicated thereafter.

4.2 Clinical trials: There are only two pivotal clinical trials for FA and the DILI Team focused on these two studies (Study 408-C-1402, Part 1 and Part 2) (**Appendix B**). Overall, just 149 subjects with this rare disease were exposed to OMX. About 90% were on OMX for >48 weeks (**Appendix C, Table A**).

Study 408-C-1402-Part 1 and 2:

Part 1 is a dose-ranging, 3:1 randomized, double-blind, placebo-controlled study in 69 FA patients for 12 weeks of treatment (includes 9 patients <18 years of age). There were 52 patients treated with OMX and 17 treated with placebo.

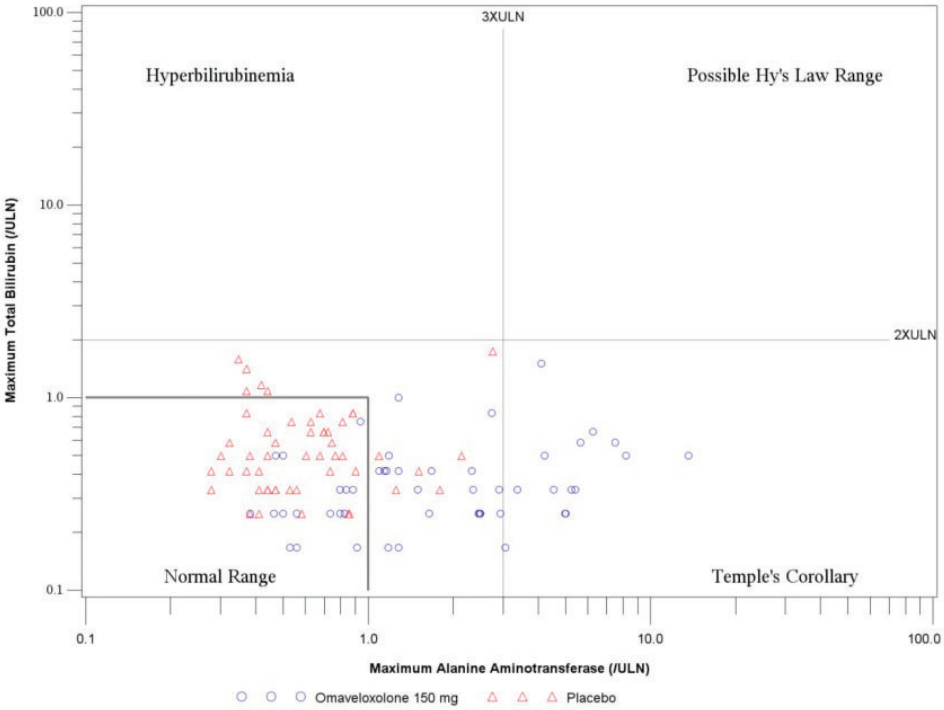
Part 2 is a double-blind, placebo-controlled study that enrolled 103 patients for up to 48 weeks of treatment. There were 51 patients treated with OMX and 52 patients treated with placebo. (See Appendix A for trial design).

Overall, there were only 51 patients exposed to OMX in the non-dose ranging, placebo-controlled portion of this study (Part 2).

Study 408-C-1402 Open-Label Extension: This study assessed the long-term safety of OMX in patients with FA who previously participated in Study 1402 Part 1 or Study 1402 Part 2. As of the 120-day safety report from Jul 28, 2022, there are 149 subjects in this study, 57 enrolled in Part 1 and carried forward with 92 subjects enrolled from Part 2 onward. Stated another way, there are 106 subjects who received PBO followed by OMX, and 43 who received OMX followed by OMX. For details on the open label exposures and retention see Appendix B.

4.3 Study level analysis for DILI:
4.3.1 *eDISH Plotting*: There were no subjects with jaundice and therefore no Hy's Law cases. However, there was an imbalance in ALT elevations. Fourteen (27%) of 51 subjects on OMX had peak ALT levels over 3x ULN compared to none of the 52 on placebo in study 408-C-1402, Part 2 (**Figure 6**).

Figure 6: eDISH for Primary Placebo-Controlled Analysis Set A (study 408-C-1402-Part 2, N=172)[19]



4.3.2 *Liver enzyme and bilirubin elevations*: Consistent with eDISH plotting, elevations in ALT (and AST) occurred only in those subjects on OMX (**Table 5**). There was no jaundice (TB >2 x ULN) in subjects on OMX. ALP levels were less than 1.5 x ULN in both arms. Gamma glutamyl transferase (GGT) elevations > 5x ULN occurred in two subjects on OMX compared to none on placebo (**Table 6**). However, these two subjects had elevated GGT levels at baseline. We did not obtain more information on these two subjects. In the absence of jaundice or marked ALP elevations, these elevations were unlikely to represent important DILI.

[19] NDA216718 (216718 - 0036 - (36) - 2022-11-30 - TRIAGE-1 /Electronic Submission/Gateway) - 408-C-1402-PT2 Report Body (#6383)

Table 5: Number and percentages of subjects with elevated liver enzymes or total bilirubin, Study 408-C-1402, (Part 2).[20]

Table 14.3.4.1.8
Number and Percentage of Patients with Elevated Liver Enzymes
Safety Population

	Placebo (N=52)	Omaveloxolone 150 mg (N=51)
ALT more than 3 x ULN	0	15 (29.4%)
ALT more than 5 x ULN	0	7 (13.7%)
ALT more than 10 x ULN	0	1 (2.0%)
ALT more than 20 x ULN	0	0
AST more than 3 x ULN	1 (1.9%)	5 (9.8%)
AST more than 5 x ULN	0	1 (2.0%)
AST more than 10 x ULN	0	1 (2.0%)
AST more than 20 x ULN	0	0
Either ALT or AST more than 3 x ULN	1 (1.9%)	16 (31.4%)
Either ALT or AST more than 5 x ULN	0	8 (15.7%)
Either ALT or AST more than 10 x ULN	0	2 (3.9%)
Either ALT or AST more than 20 x ULN	0	0
Either ALT of AST more than 5 x ULN for more than 2 consecutive weeks	0	0
ALP more than 1.5 x ULN	0	0
TBL more than 2 x ULN	0	0
AST or ALT more than 3 x ULN with an associated TBL more than 1.5 x ULN	0	0
AST or ALT more than 3 x ULN with an associated TBL more than 2 x ULN	0	0

ULN = Upper Limit of Normal

Table 6: Number and percentages of subjects with elevated gamma glutamyl transferase (GGT), Study 408-C-1402, (Part 2)[21]

Parameter (units) Treatment Group Baseline Category	Highest On-Treatment Value <=ULN	 >ULN to <5xULN	 >=5xULN
Gamma Glutamyl Transferase (U/L)			
Placebo (N=52)			
<=ULN (n=51)	49 (96.1%)	2 (3.9%)	0
>ULN to <5xULN (n=1)	0	1 (100%)	0
>=5xULN (n=0)	0	0	0
Omaveloxolone 150 mg (N=51)			
<=ULN (n=49)	44 (89.8%)	5 (10.2%)	0
>ULN to <5xULN (n=2)	0	0	2 (100%)
>=5xULN (n=0)	0	0	0

ULN = Upper Limit of Normal

4.4 Case level analysis: The DILI Team assessed all 14 subjects exposed to OMX that fell in Temple's Corollary (ALT >3x ULN). There were no hospitalizations or deaths, and all subjects fully? recovered. We assessed all 14 cases as only possible DILI due to OMX (**Table 7**). All but two subjects (12/14) had a significant decline in their transaminases or fully recovered while still on OMX. The other two subjects had OMX stopped early in the course of these elevations. If DILI occurred, then liver adaptation was common. We also felt the clinical presentation and pattern of aminotransferase

[20] NDA216718 (216718 - 0036 - (36) - 2022-11-30 - TRIAGE-1 /Electronic Submission/Gateway) - 408-C-1402-PT2 Report Body (#4277)
[21] NDA216718 (216718 - 0036 - (36) - 2022-11-30 - TRIAGE-1 /Electronic Submission/Gateway) - 408-C-1402-PT2 Report Body (#4280)

change in 12 subjects could be consistent with benign mRNA expression, which we do not consider DILI. The two other cases had competing etiologies of viral infection with enteritis and possible biliary disease (cholelithiasis). The pattern of injury was typically hepatocellular, and latency was short (median 13 days, range 4 to 28). AP and TB were remarkably normal for all 14 cases.

Table 7: Subjects with at least possible DILI due to OMX[22]

#	ID	Causality Score*	Alternate diagnosis	Studies	Age (yr)	Sex	Race	Symptoms	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)~	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak (ALT)**	R value peak (AST)**
1	(b) (6)	4	viral infection	1402 Part 2 + Ext	20	M	White	Yes	No	16	-4	749	205	129	0.6	17.42	5.69
2		4	mRNA induction	1402 Part 1 + Ext	16	M	White	No	No	4	-80	298	111	129	0.5	6.93	3.08
3		4	mRNA induction	1402 Part 2 + Ext	18	F	White	Yes	No	11	-329	278	138	129	0.8	6.47	3.83
4		4	bilary disease	1402 Part 2 + Ext	35	M	White	Yes	No	14	-328	322	147	129	0.6	7.49	4.08
5		4	mRNA induction	1402 Part 2 + Ext	23	F	White	No	No	14	-321	85	87	129	0.2	1.98	2.42
6		4	mRNA induction	1402 Part 2 + Ext	36	M	White	No	No	13	-322	269	89	129	0.8	6.26	2.47
7		4	mRNA induction	1402 Part 1 + Ext	22	F	White	No	No	7	-77	221	82	129	0.2	5.14	2.28
8		4	mRNA induction	1402 Part 2 + Ext	22	F	White	No	No	14	-318	192	87	129	0.2	4.47	2.42
9		4	mRNA induction	1402 Part 2	30	F	White	Yes	No	14	-2	195	94	129	0.3	4.53	2.61
10		4	mRNA induction	1402 Part 1 + Ext	24	M	White	No	No	6	-77	281	135	129	0.3	6.53	3.75
11		4	mRNA induction	1402 Part 1 + Ext	37	M	White	No	No	8	-77	262	97	129	0.4	6.09	2.69
12		4	mRNA induction	1402 Part 1 + Ext	30	M	White	No	No	7	-82	286	85	129	0.4	6.65	2.36
13		4	mRNA induction	1402 Part 2 + Ext	18	F	White	Yes	No	13	-320	178	103	129	0.3	4.14	2.86
14		4	mRNA induction	1402 Part 2	20	F	White	No	No	28	-102	184	73	129	0.3	4.28	2.03
				mean	*25.1*					*12*	*-174*	*271*	*110*	*129*	*0.4*	*6.3*	*3.0*
				std. dev	*6.9*					*6*	*132*	*146*	*34*	*0*	*0.2*	*3.4*	*1.0*
				median	*22.5*					*13*	*-92*	*266*	*96*	*129*	*0.4*	*6.2*	*2.7*
				max	*37*					*28*	*-2*	*749*	*205*	*129*	*0.8*	*17.4*	*5.7*
				min	*16*					*4*	*-329*	*85*	*73*	*129*	*0.2*	*2.0*	*2.0*

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^For purposes of R-value calculations, the ULN (129) was imputed of AP never rose to > ULN

** ULNs used for R-values: ALT 43 U/L, AST 36 U/L, AP 129 U/L, TB 1.2 mg/dL

~Negative day values fmeans the drug continued for that many days after injury onset.

Cases of interest: The first two cases are quite similar. We present both to emphasize this pattern of aminotransferase change that was common in the 14 subjects, and similar to cases observed with bardoxolone use, which may reflect either adaptation or benign mRNA expression of ALT and AST. The third case is a variation on this enzyme elevation pattern.

Subject (b) (6) (Study 408-C-1402 Part 1 and Extension)

Summary: This 37-year-old white, non-Hispanic or Latino male patient enrolled in Study 408-C-1402-Part 1 to receive OMX 300 mg for FA.

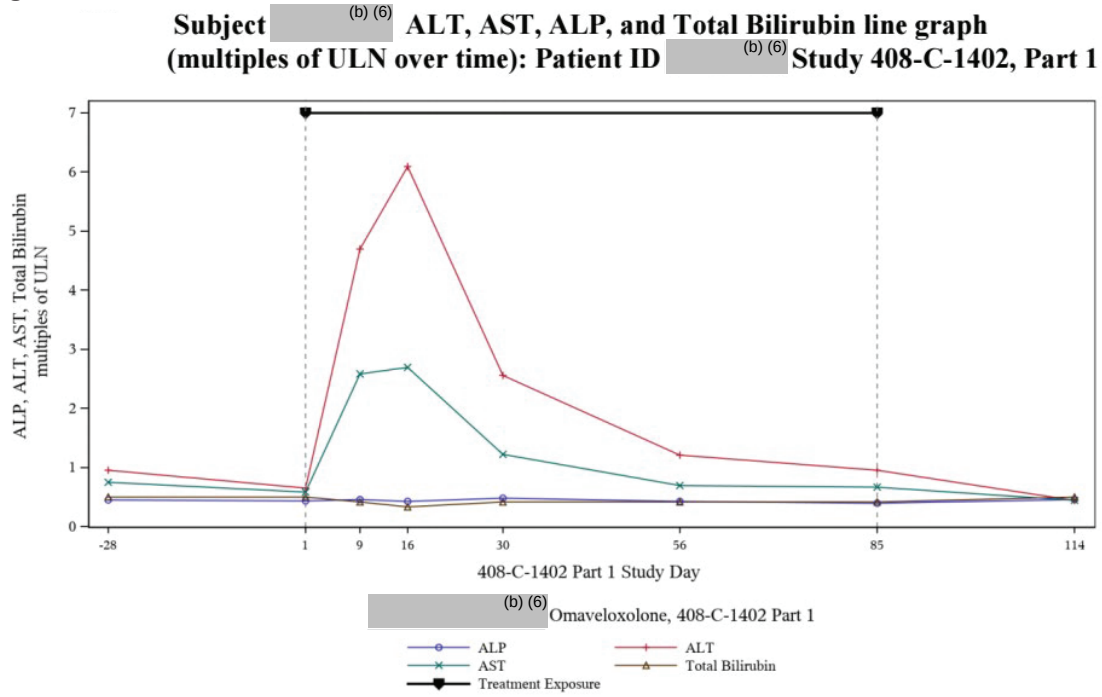
At baseline, past medical and medication history were non-contributary; no alcohol intake was provided. ALT was 28 U/L, AST 21 U/L, ALP 56 U/L and TB 0.6 mg/dL. The subject started OMX 300 mg/d on (b) (6) in part 1 of the study. The dose was not escalated or decreased throughout part 1. The subject had an asymptomatic rise in ALT and AST (202 U/L and 93 U/L) eight days after starting study drug. OMX was

[22] From DILI Team Access database and Excel spreadsheet

continued without dose-reduction. Enzymes peaked 15 days after initiating OMX, but then declined and returned to normal following the end of treatment on [redacted] (b) (6), Day 85 (**Figure 7**). There was no evaluation testing for other causes.

This subject went on to enter the extension study on [redacted] (b) (6), receiving OMX 150 mg/d. Enzymes again rose mildly (1.5 x ULN for ALT only) but then returned to normal with continued OMX use. (Extension study data not shown.) The applicant did not conduct an evaluation for these transaminase elevations in the extension study either.

Figure 7:[23]



Assessment: This is possible DILI with adaptation versus benign gene expression. Even though evaluation testing for other causes was not performed, other causes don't seem likely due to the positive rechallenge early in the extension study (extension study liver chemistry data not shown), suggesting an OMX as the likely cause. This pattern of early enzyme elevation with significant decline while on drug followed by decline to subject baseline after stopping drug is also like what was observed in the bardoxolone trials (NDA 215484)[24]

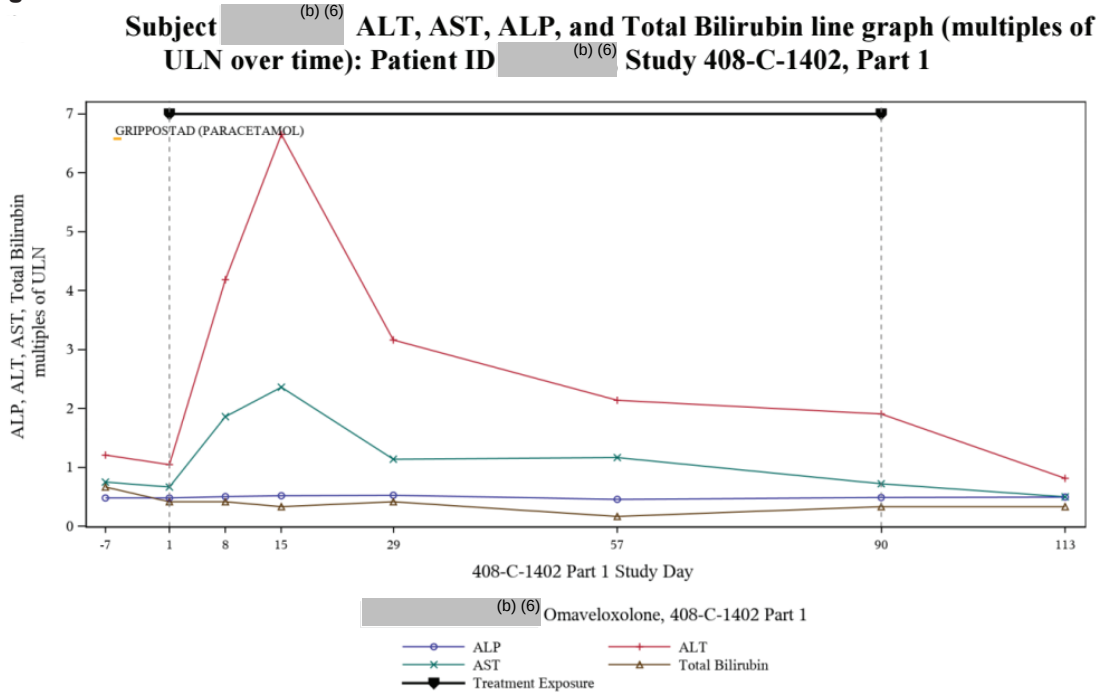
Subject [redacted] (b) (6) (Study 408-C-1402 Part 1 and Extension)

Summary: This 30-year-old white, non-Hispanic or Latino male subject enrolled in Study 408-C-1402-Part 1 to receive OMX 300 mg for FA.

[23] NDA216718 (216718 - 0024 - (24) - 2022-08-12 - ORIG-1 /Clinical/Response To Information Request) - Response to DILI Case Level Data Information Request dated 2022-06-27 (#61)
[24] (DARRT session needs to be opened first for link to work)
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80616726

At baseline, his medical history included hypercholesterolemia. He was on no medications. Alcohol history was not provided. ALT was 45 U/L, AST 24 U/L, ALP 62 U/L and TB 0.5 mg/dL. He started OMX 300 mg/d without escalation on (b) (6) (Day 1). He had an asymptomatic rise in ALT and AST (180 U/L and 67 U/L) on (b) (6) (b) (6) (Day 8). AP and TB remained normal throughout. OMX was continued. ALT and AST peaked 14 days after OMX was initiated but thereafter fell by >50% within weeks. End-of-treatment occurred on (b) (6) (Day 90). Enzymes did not return to normal baseline until 23 days following EOT. There was no evaluation testing for other possible causes. This subject also entered the extension trial on (b) (6), receiving OMX 150 mg/d. ALT and AST rose again but not as high and plateaued to just over 1x ULN for ALT despite continued long- term use of OMX (**Figure 8**). (Extension study liver chemistry data not shown)

Figure 8:[25]



Assessment: As with the previous case, we assessed this event as possible DILI with adaptation versus benign gene expression. Though no evaluation testing for other etiologies was done, other causes do not compete well because the slight positive rechallenge in the extension study suggests this is OMX- related.

Subject (b) (6) (408-C-1402 Part 2 and Extension)

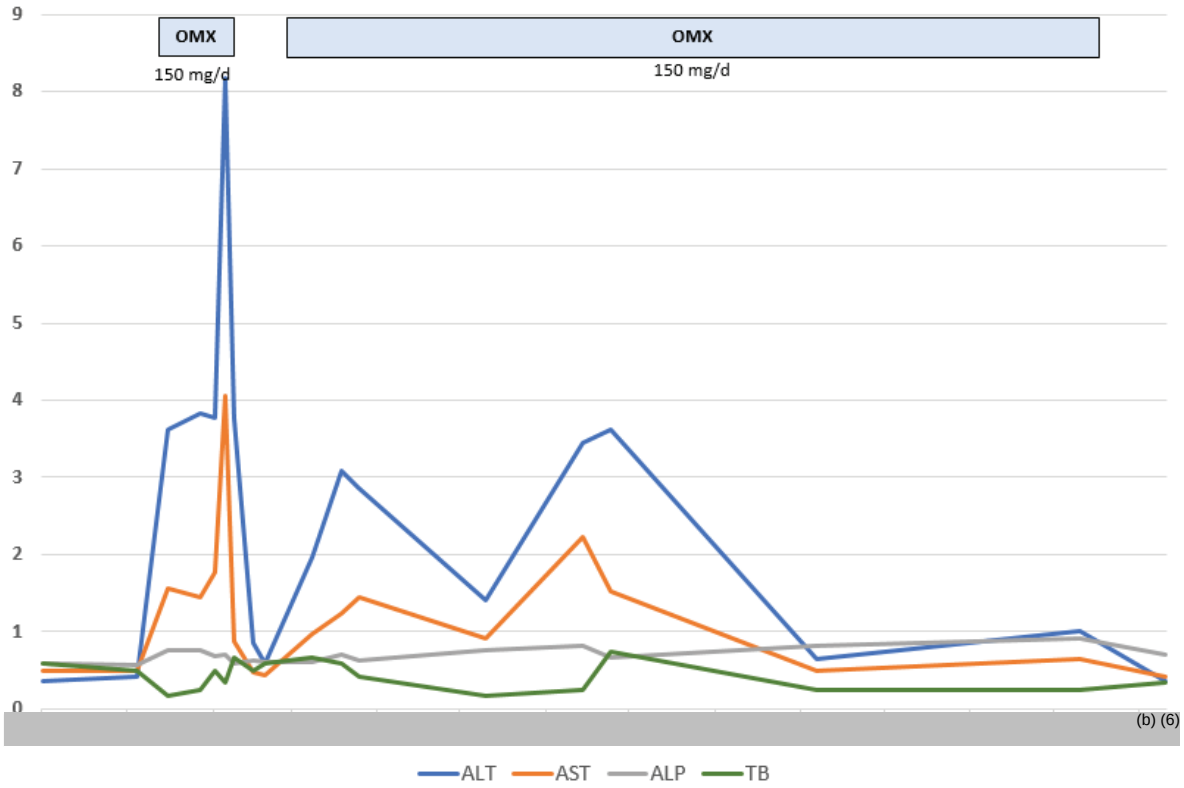
Summary: This 18-year-old white, non-Hispanic female enrolled in Study 1402 Part 2 to receive OMX 150 mg for FA.

[25] NDA216718 (216718 - 0024 - (24) - 2022-08-12 - ORIG-1 /Clinical/Response To Information Request) - Response to DILI Case Level Data Information Request dated 2022-06-27 (#66)

At baseline, medical and medication history were non-contributory. No alcohol intake information was given. At baseline ALT was 22 U/L, AST 22 U/L, ALP 115 U/L and TB 0.6 mg/dL.

The subject started OMX 150 mg/d on (b) (6) (Day 1). On (b) (6) (Day 11), she experienced an asymptomatic rise in ALT and AST (123 U/L and 53 U/L). AP and TB remained normal throughout. OMX was continued, but on (b) (6) (Day 21), her ALT rose to 278 U/L and AST to 138 U/L. She also had mild fatigue on (b) (6), and OMX was held from (b) (6), to (b) (6), when it was restarted. While the OMX was held, ALT and AST fell quickly to normal. Upon restarting, ALT and AST rose again but not as high. The transaminases had an up and down pattern before falling to around ULN, but not back to baseline while the subject was still on OMX. When OMX was finally stopped at the end of treatment, the enzymes fell to baseline (**Figure 9**). There was no evaluation testing for other causes. The subject then entered the extension study, and ALT rose to 1.5 x ULN on Day 29. The next test for ALT was not drawn for three years, and it was normal. The subject is still on OMX. (Extension study liver chemistry data not shown)

Figure 9: Liver enzyme and TB line graph for subject (b) (6) [26]



[26] Created by DILI Team from Table 6 of Clinical Information Amendment, 1.11.3, NDA216718 (216718 - 0024 - (24) - 2022-08-12 - ORIG-1 /Clinical/Response To Information Request) - Response to DILI Case Level Data Information Request dated 2022-06-27 (#20)

Assessment: This case was assessed as possible DILI with adaptation due to appropriate latencies and washout. However, gene expression may be an alternative explanation. The rapid decline after the first peak argues against DILI. Despite the sawtooth pattern after restarting OMX, the overall enzyme pattern is similar to subjects (b) (6) and (b) (6) presented above.

5.0 Assessment & Recommendations

5.1 Assessment: Omaveloxolone (OMX) is an oral small molecule that activates Nrf2 for the treatment of Frederick's Ataxia (FA). Nrf2 is a transcription factor that induces expression of many genes involved in protecting cells from inflammation and oxidative stress. Nrf2 impairment is hypothesized to be critical to FA pathophysiology, hence the rationale to activate Nrf2.

Non-clinical data do not suggest a strong risk for DILI, even though OMX is metabolized by the liver to many metabolites excreted in feces. There is no evidence that OMX inhibits transporters of concern, nor evidence for mitochondrial toxicity. There is no time-dependent inhibition of CYP3A4, the primary metabolizing CYP for OMX. There was minimal liver necrosis and aminotransferase elevation in rats, but other animal studies did not show similar findings. Necropsy demonstrated biliary tract and increased liver weight which the applicant attributed to on-target glutathione expression. In vitro experiments suggest OMX induced off-target ALT and AST gene expression that may confound the diagnosis of DILI. Enhanced mRNA aminotransferase expression has also observed with another Nrf2 activator, bardoxolone (NDA 215484) which was previously reviewed by the DILI Team.[27]

Two of the three Nrf2 activators marketed (monomethyl fumarate and diroximel fumarate) have Warnings and Precautions labeling for hepatotoxicity that arose from the results of post-market findings. While these agents also work through the Keap protein, they are structurally quite different from OMX and bardoxolone. Thus, we do not think that OMX would produce reactive metabolites similar to the fumarate-based agents. Reactive metabolite formation is the most common DILI pathophysiologic pathway.

No cases of jaundice, and no Hy's law cases were seen in the clinical trials. There was no evidence of cholestasis in trial subjects, but the trials for FA are quite small (less than 60 patients in the placebo-controlled study phase). Thus, the NDA is under-powered to detect a signal for severe DILI, yet there were more aminotransferase elevations seen with OMX. Close examination of the cases suggests that benign off-target increases in ALT and AST gene expression and DILI with adaptation are the main competing reasons to account for these transient increases in aminotransferases. The enzyme elevation patterns are consistent with rapid gene expression with later decline while on drug. In cases where OMX was stopped, aminotransferases tended to fall

[27] (DARRT session needs to be opened first for link to work)
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80616726
[27] NDA216718 (216718 - 0035 - (35) - 2022-10-26 - ORIG-1 /Clinical/Response To Information Request) - RTA400-R-1120

rapidly which would be consistent with enhanced gene (mRNA) expression and subsequent decline based on ALT and AST half-lives of 47 and 17 hours, respectively,[28] rather than hepatotoxicity. Bardoxolone produced similar aminotransferase patterns. However, the in vitro concentrations used to show ALT and AST mRNA increase were substantially higher than expected serum concentrations in vivo. So, if off-target gene expression is not explanatory, then DILI is the most likely cause. Fortunately, all subjects with transaminase elevations recovered, and most had declines in their transaminase enzyme without stopping OMX suggesting host-DILI adaptation followed by a benign course. Nevertheless, prescribers should not presume benign adaptation or gene expression are the only two explanations possible for transaminase excursions. Lastly, failure for a subject to result in ALT returning to baseline while on OMX could also be due to chronic, low-level liver injury.

Overall, we can support approval for the FA treatment because of the unmet medical need and lack of clear and significant liver-injury. The label would need to describe the enzyme elevations that will likely occur with large-scale use. Because the clinical trials are small, monitoring may be justified during the first three months of OMX use to confirm aminotransaminases decline while a patient is still taking the drug. If such a decline does not occur or TB rises, then OMX should be stopped. Post-market studies assessing both acute and chronic liver injury should be considered. Studies using markers recently developed for more specific DILI detection (e.g., glutamate dehydrogenase, miR-122) may give insight as to whether the aminotransferase elevations are from gene expression or true liver injury.[29] Our specific recommendations are below.

5.2 Recommendations

1. Support approval if efficacy requirements are met and there are no other safety issues.
2. Labeling should describe the incidence and pattern of liver enzyme elevations
3. Labeling should include monitoring baseline liver enzymes and bilirubin.
4. Consider labeling for liver enzyme and bilirubin monitoring monthly for the first three months and as clinically indicated thereafter. If liver enzymes do not fall substantially or bilirubin rises, OMX should be stopped.
5. Consider post market studies for assessment of possible acute and chronic liver injury due to OMX.
6. Consider checking stored serum samples (if available) in the 14 subjects with ALT >3 x ULN for GLDH and miRNA-122. If these analytes were not elevated, then this would lessen concerns that the elevated serum levels of ALT and AST reflect DILI events and strengthen an interpretation that the increases in the hepatocyte expression of ALT and AST mRNA induced by omaveloxolone are isolated without pathological inference. If there are no stored sera then a small

[28] Woreta TA, et al. Evaluation of Abnormal Liver Tests. *Med Clin N Amer*. 2014; 98:1-16, http://dx.doi.org/10.1016/j.mcna.2013.09.005

[29] Church RJ, et al. Candidate biomarkers for the diagnosis and prognosis of drug-induced liver injury: An international collaborative effort**.** Hepatology.2019; 69: 760-73, https://doi.org/10.1002/hep.29802

post-market study to measure levels of these indicators in patients on OMX should be considered.

Ling Lan -S
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Paul H. Hayashi, MD, MPH
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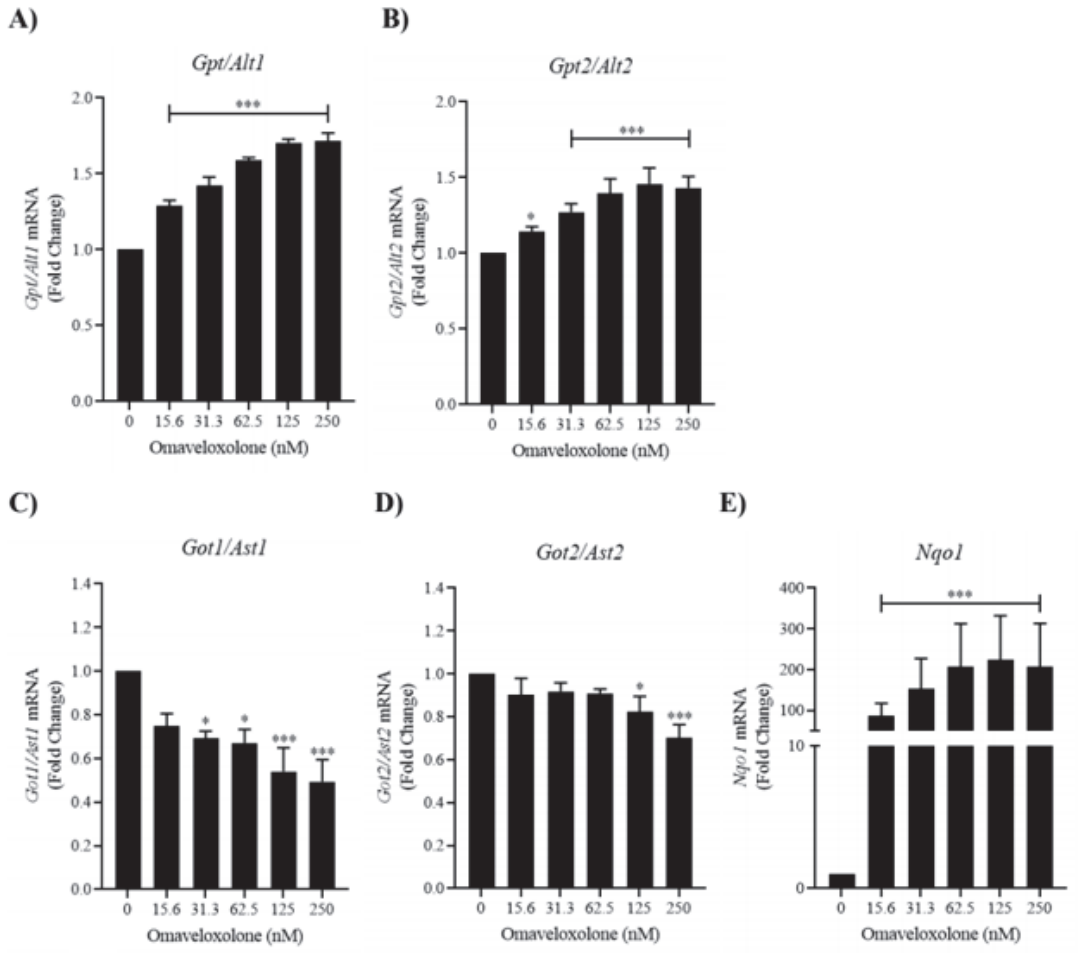
Date: 2022.12.05 16:22:07 -05'00'

Frank A. Anania, MD, FACP, AGAF, FAASLD
Acting Director, Division of Hepatology and Nutrition
CDER/OND

Appendix A: Effect of OMX on Aminotransferase mRNA in Mouse Macrophage Cell line. Nqo1 is used as an on-target positive control because this gene codes for a detoxifying protein and is known to be induced by OMX[30]



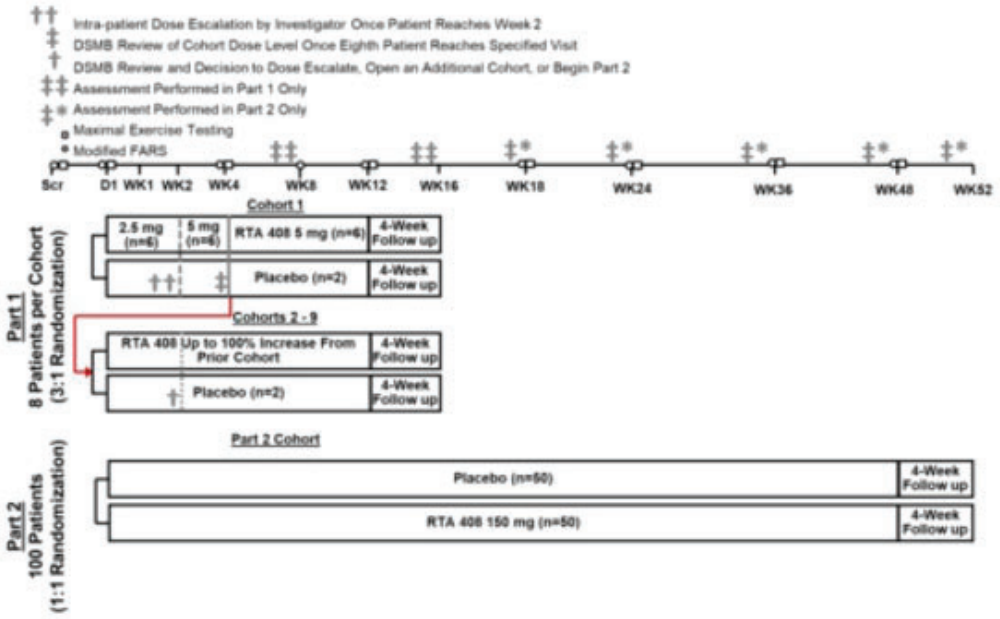
Effect of Omaveloxolone on Aminotransferase Gene Expression in the RAW 264.7 Mouse Macrophage Cell Line

RAW 264.7 cells were treated with omaveloxolone or vehicle for 17 hours. Relative mRNA levels of *Gpt/Alt1* (**A**), *Gpt2/Alt2* (**B**), *Got1/Ast1* (**C**), *Got2/Ast2* (**D**), and *Nqo1* (**E**) were assessed by RT-qPCR. Data are mean ± SD of three replicate experiments and are shown as fold change relative to vehicle-treated control. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ vs. vehicle-treated control by repeated measures one-way ANOVA and Dunnett's multiple comparison test.

[30] NDA216718 (216718 - 0012 - (12) - 2022-06-21 - ORIG-1 /Quality/Response to Information Request) - RTA400-R-2002 (#24)

Appendix B: Study Design for 408-C-1402-Part 1 and 2[31]

Schema for Part 1 and Part 2 Evaluation of RTA 408 in Patients with Friedreich's Ataxia



[31] NDA216718 (216718 - 0012 - (12) - 2022-06-21 - ORIG-1 /Quality/Response To Information Request) - 408-C-1402 Protocol v11_UK (#30)

Appendix C: Updated subject enrollment and retainment in Extension study

Table A:

Study Drug Exposure in Study 1402 Extension

Interim Database Lock	Weeks Category	Maximum Patient Weeks of Exposure n (%) Placebo – Omav N=106	Omav-Omav N=43	Overall Omav N=149
17 Aug 2021	>48	92 (86.8)	40 (93.0)	132 (88.6)
	>72	85 (80.2)	40 (93.0)	125 (83.9)
	>96	68 (64.2)	30 (69.8)	98 (65.8)
24 March 2022	>48	93 (87.7)	40 (93.0)	133 (89.3)
	>72	88 (83.0)	40 (93.0)	128 (85.9)
	>96	85 (80.2)	40 (93.0)	125 (83.9)
	>120	79 (74.5)	36 (83.7)	115 (77.2)
	>144	50 (47.2)	19 (44.2)	69 (46.3)
	>168	5 (4.7)	6 (14.0)	11 (7.4)

Abbreviations: Omav=omaveloxolone
Sources: Study 1402 Extension 2021 Table 14.1.6.3; Study 1402 Extension 2022 Table 14.1.6.3

ISS Set D: the long-term safety set is defined by the patients who randomized to OMX in Study 1402 Part 2, completed Study 1402 Part 2, and enrolled in the Study 1402 Extension. Through Mar 24, 2022, there are 51 subjects in this cohort. (Table 7) Retainment is 80% (40 of 51).

Table B: 120-day safety came in Jul 28, 2022, and includes updates on ISS Set D.

Exposure in the Long-Term Safety Study 1402 Subgroup (ISS Set D)

Interim Database Lock	Median Patient Years Exposure (min, max)	Maximum Patient Weeks of Exposure Category	n (%)[b]	Patients with ≥90% Compliance[a] n (%)
17 Aug 2021	2.88 (0.0, 3.7)	>48	44 (88.0%)	31 (62.0%)
		>52	42 (84.0%)	
		>72	41 (82.0%)	
		>96	40 (80.0%)	
		>192	0	
		Missing	1	
24 March 2022	3.64 (0.0, 4.3)	>48	44 (88.0%)	35 (70.0%)
		>52	42 (84.0%)	
		>72	41 (82.0%)	
		>96	40 (80.0%)	
		>192	20 (40.0%)	
		Missing	1	

Abbreviations: ISS=Integrated Summary of Safety; max=maximum; min=minimum.
[a] Percentages are based on the number of nonmissing observations.
[b] Percentages are based on the number of nonmissing observations in patients with at least 48 weeks of exposure.
Note: For patients who started omaveloxolone in Study 1402 Part 2 and entered Study 1402 Extension, exposure and compliance were calculated across both studies. Extension exposure was based on the imputed date of end of treatment, based on the last contact date of the patient for patients continuing study treatment in Study 1402 Extension. This may be different from the calculation of exposure in the double-blind period, which relied on dates of returned kits.
Source: 2021 ISS Table 5.1.3; 2022 ISS Table 5.1.3

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/s/

PAUL H HAYASHI
12/05/2022 05:42:44 PM

Clinical Inspection Summary

Date	11/08/2022
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. (Acting) Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Brenda Reggettz, Regulatory Project Manager Veneeta Tandon, Ph.D., Clinical Reviewer Emily Freilich, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #	216718
Applicant	Reata Pharmaceuticals, Inc.
Drug	Omaveloxolone
NME	Yes
Proposed Indication	Treatment of Friedreich's ataxia
Consultation Request Date	4/1/2022
Summary Goal Date	9/30/2022, extended to 10/14/2022, 11/18/2022
Priority/Standard Review	Priority
Action Goal Date	2/28/2023
PDUFA Date	11/30/2022, extended to 2/28/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Giunti, Lynch, and Perlman were inspected in support of this NDA, covering Protocol 408-C-1402 (Parts 1 and 2). The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

Omaveloxolone capsules have been developed under IND 122349 for the treatment of Friedreich's ataxia. Currently, there are no approved treatments for this inherited disorder. The sponsor has submitted the results of Protocol 408-C-1402, a Phase 2 study, to support NDA 216718 for the efficacy and safety of omaveloxolone in the treatment of Friedrich's ataxia.

Protocol 408-C-1402

Title: "A phase 2 study of the safety, efficacy, and pharmacodynamics of RTA 408 [omaveloxolone] in the treatment of Friedreich's ataxia"

Subjects: Part 1: 69 subjects; Part 2: 103 subjects

Sites:

- Part 1: 8 sites in United States (6), Western Europe (1), and Australia (1)
- Part 2: 11 sites [8 as in Part 1, with additional sites in United States (1), Western Europe (2)]

Study Initiation and Completion Dates:

- Part 1: 1/8/2015 – 6/13/2017
- Part 2: 10/20/2017 – 10/31/2019

This Phase 2 study was divided into two parts. Part 1 was a randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, tolerability, and pharmacokinetics in subjects with Friedreich's ataxia and to select a dose of omaveloxolone for Part 2 of the study, which ended being 150 mg. Part 2 was a randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of omaveloxolone 150 mg in subjects with Friedreich's ataxia.

Main eligibility criteria included males or females, ≥16 and ≤40 years of age; genetically confirmed Friedreich's ataxia; modified Friedreich's Ataxia Rating Scale (mFARS) score ≥20 and ≤80 (average of two values collected at screening and Day 1 and must be within 4.5 points of each other); no changes to their exercise regimen within 30 days prior to Day 1; estimated glomerular filtration rate (eGFR) >60 mL/min; left ventricular ejection fraction ≥40%; and B-type natriuretic peptide (BNP) ≤200 pg/mL.

Part 1 – Dose finding

Screening Phase (Day -28 to -1)
Subjects were screened for study eligibility. Assessments included, but were not limited to, labs, echocardiogram, clinical assessments including mFARS, and maximal exercise test. Procedures such as cardiac MRI and muscle needle biopsy were optional.

Double-Blind Phase (Day 1 to Week 12)
Up to 9 cohorts were planned to be enrolled. For each cohort, subjects were randomized (3:1) to omaveloxolone or placebo.

First cohort (n = 9): subjects were randomized to omaveloxolone 2.5 mg or placebo. After Week 2, subjects randomized to omaveloxolone had their dose increased to 5 mg unless a dose-limiting toxicity was reported (the first cohort receiving 2.5 mg was the only cohort to have a dose increase). After the last subject completed Week 4, the data safety monitoring board (DSMB) and sponsor reviewed safety data to inform dosing in the next cohort.

Second and subsequent cohorts (n = 8/cohort): After the last subject completed the Week 2 visit, the DSMB reviewed safety data and recommended the dose for the next cohort. The following dose cohorts were ultimately evaluated: 2.5 mg/5 mg, 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, and 300 mg.

Follow-up Visit (Week 16)
A follow-up visit for safety assessments occurred 4 weeks after the last dose of investigational product.

Part 2 – Efficacy

Screening Phase (Day -60 to -1)
Subjects were screened for study eligibility. Assessments included, but were not limited to, labs, echocardiogram, foot x-ray and pes cavus assessment, clinical assessments including mFARS, and maximal exercise test.

Double-Blind Phase (Day 1 to Week 48)
Subjects were randomized (1:1), stratified by pes cavus status (yes/no), to:

- Omaveloxolone 150 mg capsule once daily
- Placebo capsule once daily

Follow-up Visit (Week 52)
A follow-up visit for safety assessments occurred 4 weeks after the last dose of investigational product.

Extension Phase
Subjects who completed Part 1 or Part 2 of the study could enter an extension phase and receive open-label omaveloxolone 150 mg once daily, to be continued until the drug was approved. Since subjects participating in Part 1 were not followed continuously in the study, a screening visit was completed to confirm eligibility for the extension phase.

The ***primary efficacy endpoint*** of Part 2 was the change from Day 1 (baseline) to Week 48 in the mFARS score for omaveloxolone vs. placebo. Secondary efficacy endpoints included the change from Day 1 (baseline) to Week 48 in the Patient Global Impression of Change (PGIC) and the Clinical Global Impression of Change (CGIC). Exploratory endpoints included the change in Friedreich's Ataxia-Activities of Daily Living (FA-ADL) score and the occurrence of falls.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, impact on efficacy, and prior inspectional history.

III. RESULTS

1. Paola Giunti, M.D.
Site #6225
Queen Square Box 143
University College London
Institute of Neurology
London, CMD, WC1N 3BG
United Kingdom
Inspection Dates: 8/15/2022 – 8/18/2022

This site did not enroll subjects in Part 1 of Protocol 408-C-1402. For Protocol 408-C-1402 Part 2, 22 subjects were screened, 8 subjects were randomized, and 7 subjects completed the double-blind phase of the study. Subject # (b) (6), randomized to omaveloxolone, withdrew from the study due to the serious adverse event of ventricular tachycardia (see below). The narrative for this SAE was included in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and efficacy endpoints.

The primary efficacy data (modified Friedreich's Ataxia Rating Scale [mFARS]), secondary efficacy data (Patient Global Impression of Change [PGIC] and Clinical Global Impression of Change [CGIC]), and exploratory efficacy data (Friedreich's Ataxia-Activities of Daily Living [FA-ADL]) were verified against the sponsor data line listings for all randomized subjects. Two discrepancies were noted for the FARS in two subjects due to errors in transcribing the data from paper source into the electronic data capture (EDC) system:

- Subject # (b) (6), randomized to omaveloxolone, had a Week 24 FARS subscore for the lower limb coordination of 6.5 on paper source and 6.0 in the sponsor data line listing.
- Subject # (b) (6), randomized to omaveloxolone, had a Week 12 FARS subscore for peripheral nervous system score of 8 on paper source and 10 in the sponsor data line listing.

Reviewer's comment: There was one discrepancy of 0.5 points noted on the Week 24 lower limb coordination subscale of the mFARS for one subject randomized to omaveloxolone. It is unlikely that this discrepancy, which occurred at a timepoint other than the Week 48 timepoint of interest, would impact the overall efficacy analysis. The other discrepancy occurred in the peripheral nervous system subscale, which is included in the FARS but not the

mFARS (primary efficacy endpoint) scale; and therefore, would not impact the mFARS score

There was no evidence of under-reporting of adverse events. The inspection confirmed that Subject # (b) (6) did not have a Week 48 mFARS assessment since this subject discontinued early due to the SAE ventricular tachycardia which was identified on the Week 4 exercise test.

During the study, subjects or caregivers completed paper diaries recording the day and time of investigational product administration. For Part 2 of the study, falls were also to be recorded in these diaries including the date, location, and relevant details (activity prior to fall, perceived cause of fall, etc.). Some, but not all, of these diary pages were collected for all 8 randomized subjects during the inspection. This reviewer verified the diary pages against the sponsor's data line listing for falls with one discrepancy noted. Subject # (b) (6), randomized to placebo, experienced a fall on (b) (6) that was not listed in the sponsor's data line listings.

Reviewer's comment: Evaluation of the frequency of falls was an exploratory objective for this study. One fall in one subject randomized to placebo was recorded in the paper diary but was not included in the sponsor's data line listings. It is unlikely that omission of one fall would impact the overall analysis for this exploratory endpoint.

2. David Lynch, M.D., Ph.D.
Site #1875
The Children's Hospital of Philadelphia
Abramson Research Center
3615 Civic Center Blvd, room 502
Philadelphia, PA 19104-4318
Inspection Dates: 7/1/2022 – 7/22/2022

At this site for Protocol 408-C-1402 Part 1, 27 subjects were screened, and 24 were randomized, all of whom completed the study. For Protocol 408-C-1402 Part 2, 38 subjects were screened, 26 were randomized, and 25 subjects completed the double-blind phase of the study. Subject # (b) (6), randomized to omaveloxolone, discontinued the study due to "withdrawal by subject" (see below).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and efficacy endpoints.

Efficacy endpoints were verified for Part 2 of Protocol 408-C-1402, the double-blind, efficacy portion of the study. The primary efficacy data, mFARS, and secondary efficacy data, PGIC and

CGIC, were verified against the sponsor data line listings for all randomized subjects; no discrepancies were identified. Additionally, exploratory efficacy data, FA-ADL, was verified against the sponsor line listings; no discrepancies were identified here either.

There was no evidence of under-reporting of adverse events for Part 1 or Part 2 of Protocol 408-C-1402. Subject # (b) (6), randomized to omaveloxolone on Day 1, experienced the SAE atrial fibrillation on Day 52 and was hospitalized, received electrical cardioversion, and was discharged the following day. In email correspondence between the sponsor and site regarding this SAE, it appears that there was a recurrence of atrial fibrillation on or around Day 65, and the subject was prescribed propafenone. In the email correspondence, the sponsor noted that propafenone was a prohibited medication per protocol. The subject and family decided to continue propafenone rather than switching to another antiarrhythmic, and the subject withdrew from the study. The site was informed of the SAE on the day it occurred and reported it to the sponsor on that same day. The narrative for this SAE is included in the NDA submission but does not include information regarding the recurrence of atrial fibrillation and initiation of propafenone on (b) (6) (per concomitant medication line listing).

Reviewer's comment: The review division may consider requesting an updated narrative for Subject # (b) (6) *to include the recurrence and treatment of atrial fibrillation.*

3. Susan Perlman, M.D
Site #1914
710 Westwood Plaza
Suite 1150
Los Angeles, CA 90095-8346
Inspection Dates: 6/27/2022 – 6/30/2022

At this site for Protocol 408-C-1402 Part 1, 7 subjects were screened, and 5 subjects were randomized, all of whom completed the study. For Protocol 408-C-1402 Part 2, 22 subjects were screened, and 15 subjects were randomized, all of whom completed the double-blind phase of the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and efficacy endpoints.

Efficacy endpoints were verified for Part 2 of Protocol 408-C-1402, the double-blind, efficacy portion of the study. The primary efficacy data, mFARS, and secondary efficacy data, PGIC and CGIC, were verified against the sponsor data line listings for all randomized subjects; no

discrepancies were identified. Additionally, exploratory efficacy data, FA-ADL, was verified against the sponsor line listings; no discrepancies were identified here either.

During the study, subjects or caregivers completed paper diaries recording the day and time of investigational product administration. For Part 2 of the study, falls were also to be recorded in these diaries, including the date, location, and relevant details (e.g., activity prior to fall and perceived cause of fall). Diary pages were collected for 10 of 15 randomized subjects during the inspection. This reviewer verified the diary pages against the sponsor's data line listing for falls, and no discrepancies were identified. Upon review of these diaries, additional information had been recorded for Subject # (b) (6), noting a visit to the ER due to "high blood pressure and chest pains" on Day 110. This subject was randomized to placebo.

Reviewer comments: Two adverse events occurring in one of 15 randomized subjects participating in Part 2 of the protocol were not reported to the sponsor. Since these unreported adverse events occurred in a subject randomized to placebo, it is unlikely that omission of this data would impact the safety analysis.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
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11/08/2022 11:04:01 AM

JENN W SELLERS
11/08/2022 11:12:22 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 216718
Submission Number	#001
Submission Date	7/7/2022
Date Consult Received	7/7/2022
Drug Name	Skyclarys (omaveloxolone)
Indication	Friedreich's ataxia
Therapeutic Dose	150 mg once daily on empty stomach
Clinical Division	DN1

Note: Any text in the review with a light background should be considered to be copied from the Applicant's document.

This review responds to your consult dated 7/7/2022 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Previous IRT reviews dated 05/24/2022 and 08/21/2021 in DARRTS;
- Investigator's brochure (SDN0013; link);
- Highlights of clinical pharmacology and cardiac safety (SDN0001; link);
- Clinical study report of Study 408-C1703 (SDN0001; link);
- Clinical study report of Study 408-C-1806 (SDN0001; link);
- Clinical study report of Study 408-C-1402 Part 2 (SDN0001; link);
- Concentration QT report (SDN0001; link).

1 SUMMARY OF FINDINGS

The effect of omaveloxolone on the QTc interval has not been adequately characterized.

The submitted clinical ECG data are not sufficient to exclude a 10-msec mean increase in the QTc interval. ECGs were collected in a drug-drug interaction (DDI) study (Study 408-C-1806) and food effect study (Study # 408-C1703). These studies are not designed to exclude small increases in the QTc interval.

- Neither study included a positive control nor had sufficiently large exposures to waive the positive control per ICH E14 Q&A 5.1.
- QTc interval was not assessed at high clinical exposures.
- High quality, digital ECGs were not collected.
- The timing of ECGs did not capture QTc effects at maximum concentrations of omaveloxolone.

The proarrhythmic potential of omaveloxolone was tested in nonclinical safety pharmacology studies. Both the hERG assay and in vivo QTc study were not conducted

under best practices (section 4.1.2) and cannot be used for an integrated nonclinical risk assessment to support clinical QTc assessment according to ICH S7B Q&A 1.1–1.2.

The Applicant has already agreed to conduct a thorough QT study which will be submitted after the PDUFA date for this NDA submission.

2 ADDITONAL COMMENTS TO THE REVIEW DIVISION

There is not a concerning proarrhythmic signal in the clinical and nonclinical data, but the data cannot be used to exclude a small increase in the QTc interval. We still recommend that the Applicant conducts their planned TQT study. We defer the timing of the TQT study submission to the Division.

3 RECOMMENDATIONS

3.1 ADDITIONAL STUDIES

See our comments in section 2.

3.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 0001 (link) from the CSS-IRT. Our changes are highlighted (addition, ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Potential to Prolong the QT interval

(b) (4)

The effect of omaveloxolone on the QTc interval has not been adequately characterized.

(b) (5)

4 APPLICANT'S SUBMISSION

4.1 OVERVIEW

4.1.1 Clinical

Reata pharmaceuticals, Inc. is developing omaveloxolone for the treatment of Friedreich's ataxia (FA), a rare genetic neuromuscular disorder, in adult and pediatric patients (>16 years). Omaveloxolone (RTA-408, TX63415, FP-190, ABT-RTA 408, A-1402484.0, BT07; MW: 554.72 g/mole; a synthetic triterpenoid-derivative) is a nuclear factor erythroid 2-like 2 (Nrf2) activators.

The recommended dose is 150 mg once daily, administered as three immediate-release 50 mg capsules. In the proposed label, omaveloxolone is contraindicated with the use of strong and moderate CYP3A4 inhibitors. Omaveloxolone should not be used in patients with (b) (4) severe hepatic impairment, and it is recommended to be taken without food.

The steady state C_{max} (CV%) following 150 mg QD is expected at 72 ng/mL (34%) with median T_{max} ~ 7–14 h and terminal half-life ~ 48 h. Subjects with moderate hepatic impairment had 83% higher C_{max} than normal hepatic function subjects (34 ng/mL vs. 62 ng/mL) following single dose of 150 mg omaveloxolone administered under fasted conditions (Study 408-C-1804, link). Patients with severe hepatic impairment had a lower C_{max} (0.7-fold) compared to the normal group. The product exhibits a positive food effect with a 4.5-fold increase in omaveloxolone exposure (C_{max}: 25 ng/mL vs. 119 ng/mL) following 150 mg single dose administration with a high-fat meal compared to that under fasted conditions (Study 408-C-1703, Part 1, link). Concomitant administration of 150 mg single dose omaveloxolone with a strong CYP3A4 inhibitor (200 mg itraconazole once daily) resulted in 2.7-fold increased exposures of omaveloxolone (C_{max}: 43 ng/mL vs. 119 ng/mL, Study 408-C-1806, Part 3; link). Concomitant use with CYP3A4 inhibitor is contraindicated and omaveloxolone is recommended to take without food in the product labeling. Therefore, the clinical worst-case exposure occurs when the drug is unintentionally administered with food, resulting in 4.5-fold increase in C_{max} compared to fasting condition.

The Applicant initially proposed to characterize the QT prolongation using their C-QT model from the open-label food effect Study 408-C1703 (link) and open-label drug-drug-interaction (DDI) Study 408-C-1806 (link). We did not agree (review on 8/24/2021) because the exposure in those two studies did not cover at least 2-fold of high clinical exposure and we recommended a TQT study. The Applicant proposed a TQT study thereafter and we found it acceptable (review on 5/24/2022). We also noted the Division indicated that the TQT study may be conducted post-approval.

Under the current NDA, the Applicant submitted their C-QT model based on the open label food effect and DDI studies (see QT assessment review in Appendix 6.1) and claimed omaveloxolone had no effect on QTcF at therapeutic dose and in clinical worst-case scenario.

Study 408-C-1703 was a phase-1, open-label, food effect (Part 1; n=16; crossover fed vs fasting at 150 mg single dose), and dose proportionality (Part 2; n=16; parallel 50 and 150

mg single dose) study with omaveloxolone in healthy subjects. The geometric mean (CV%) Cmax of 119 ng/mL (45.6) was observed with the highest dose studied (i.e., 150 mg single dose, under fed conditions; n=15, median (range) Tmax = 5 (2 - 8) h). ECG (12-lead) were collected at pre-dose, 3, and 24 h post dose.

Reviewer's comment*: ECGs do not capture Tmax; therefore, QTc data from this study is not informative.*

Study 408-C-1806 was a phase-1, open-label, drug interaction study (4-part; Part 1: cocktail study; part 2: gemfibrozil; Part 3: itraconazole; Part 4: verapamil) with omaveloxolone in healthy subjects. The highest exposure achieved was concomitant administration of omaveloxolone with itraconazole (200 mg itraconazole QD + 150 mg omaveloxolone single dose), resulting in geometric mean (CV%) Cmax of 116 ng/mL (70%) (Part 3, under fasting conditions). In part 3, ECG were collected at pre-dose, 4, 12, 24, and 48 h post dose on Day 1 and Day 13.

Reviewer's comment*: ECGs only capture Tmax of omaveloxolone alone and not when co-administered with itraconazole; therefore, QTc data from this study is not informative.*

For both studies, 12-lead ECGs were recorded and read locally. Triplicate ECGs, approximately 1 minute apart, were obtained at nominal time points ± 30 minutes. Digital ECGs were not acquired, and Applicant submitted paper scans of the waveforms.

In both studies, the maximum exposure covered the clinical exposure but not the high clinical exposure which is 4.5-fold of the anticipated steady state Cmax (71.5 × 4.5 = 321.75 ng/mL).

Both in vitro hERG assay and in vivo study showed deviations from the best practice recommendations according to the new ICH S7B Q&As and may not be included in the integrated non-clinical risk assessment to support ICH E14 5.1 or 6.1.

Given the limitation of both clinical and nonclinical studies, the current QT assessment is insufficient. We request the Applicant to conduct a TQT study in the postmarket setting. Since food has possible cardiac effects, i.e., literature studies suggest a shortening of the QTcF interval, in our analysis we excluded Study 408-C-1703 (food effect study) due to the difficulty to interpret the results without a placebo control. Since verapamil also has known cardiac effects, we also did not include Part 4 from Study 408-C-1806 (DDI) in our analysis.

The IRT performed by-time and C-QT analysis for Study 408-C-1806 Part 2 and 3, separately, to avoid the complexity of pooling across drug combinations (Day 1 and Day 13 were pooled for C-QT, but not for by-time). In addition, due to the insufficiency of the food effect, DDI and nonclinical studies, safety assessment was also performed on Study 408-C-1402 Part 2, (b) (4)

4.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the CP table (link)

Cardiac safety was assessed in GLP-compliant safety pharmacology studies, including an in vitro Human ether-À-go-go related gene (hERG) assay (Study RTA408-P-1114) and an in vivo study in monkeys (RTA408-P-1113). Cardiac safety was also assessed in the 9-

month monkey GLP toxicity study with ECGs at pre-test, Week 13, and Week 39. In the hERG assay, superfusion of omaveloxolone at concentrations of 0.75 and 1.2 µM produced minimal concentration-dependent blockage of hERG current, with approximately 6.73% ± 4.24% and 21.5% ± 5.4% inhibition, respectively, compared to 0.675% ± 2.120% for the vehicle control (physiological saline solution with 0.1% acetone). The 0.75 µM omaveloxolone concentration corresponds to approximately 188-times the steady state maximum free plasma drug concentration (Cmax,ss) in patients with FA administered the proposed therapeutic dose of 150 mg QD (i.e., 4.00 nM with 97% protein binding). In the monkey cardiovascular safety pharmacology assay, no effects on cardiovascular function were observed up to the highest single oral dose evaluated (100 mg/kg), which corresponds to approximately 5-times the Cmax in patients with FA after a single administration of the planned therapeutic dose of 150 mg (i.e., 41.1 ng/mL).

Reviewer's assessment: *The Applicant evaluated the effects of RTA408 (omaveloxolone) on hERG current, a surrogate for IKr that mediates membrane potential repolarization in cardiac myocytes. The GLP hERG study report (RTA408-P-1114) describes the potential effects of RTA408 on the hERG current in HEK293 cells. The hERG current was assessed at near physiological temperature (35.2-35.9°C), using a step-step voltage protocol (from a holding potential of -80 mV to a depolarizing step to +40 mV for 2 seconds, followed by a repolarizing c step to –50 mV for 1.5 seconds) that is different to the recommended hERG current protocol by the FDA (link). The reviewer does not expect protocol differences to impact hERG current pharmacology The positive control (0.1µM cisapride) inhibited hERG potassium current by 78%. Samples of the test article solutions collected from the superfusate were analyzed for concentration verification. The reviewer doesn't know whether the samples were collected from the chamber or not. The results from the sample analysis indicated that measured concentrations were with 100% ± 10% of nominal concentrations; thereby meeting the acceptance criteria and measured concentrations were used to describe drug effects. No reference drugs were included in this study.*

RTA408 inhibited the hERG currents by 6.7 % and 21.5% at 0.75µM and 1.2 µM, respectively. The estimated IC50 for the inhibitory effect of RTA408 on hERG current was greater than 1.2 µM.

The hERG safety margins of RTA408 on hERG current are summarized below:

Table 1: Safety Margin of RTA 408on hERG Current

	Cmax (ng/mL)	*Protein Binding*	*Free Cmax (ng/mL)*	*hERG IC50 (µM)*	*Mol Weight (g/mol)*	*Safety Margin (Ratio)*
Omaveloxone (RTA408)	*322*	*97%*	*9.65*	*>1.2 µM (21.5%)*	*554.72*	*>69x*

The POP-PK predicted mean Cmax at steady-state was ~71.5 ng/mL. The high clinical exposure will be 1.83x to 4.5x (131 ng/mL to 322 ng/mL) of the Cmax,ss under moderate hepatic impairment, with a strong CYP3A4 inhibitor or under food effects.

The assessment of the hERG assay is summarized below:

Table 2: Evaluation of In Vitro hERG Assay

Best Practice Element	***Deviation/Issue***	***Impact of Deviation/Issue***
Temperature (35-37°C)	*None*	
Voltage Protocol	*lack of steps in the voltage protocol to enable cell health monitoring throughout the experiment*	*The input resistance of the cell cannot be assessed*
Recording Quality	*None*	
IC50 Calculation	*Only two concentrations were tested*	*IC50 cannot be determined*
Concentration Verification	*Sample collection site are unclear*	*Pre-chamber sample collection may result in underestimated the inhibition.*
Positive Control	*Only one concentration of positive control was tested*	*The potency (i.e., IC50 value) of the positive control drug cannot be determined*
Negative Control	*None*	
Good Laboratory Practice	*None*	

The in vivo monkey study RTA408-P-1113 (link) assessed the potential effects of RTA408 on ECG parameters following a single dose (10, 30 or 100 mg/kg) oral administration of RTA408 in conscious cynomolgus monkeys. There was a 14-day washout period between administrations, until each animal received all treatments. ECG parameters (QRS duration and the RR, PR, and QT intervals) were monitored continuously from at least 2 hours predose until at least 24 hours postdose. No PK data were conducted in this study. However, PK data may be inferred from another TK study (link) with the same doses in monkeys. The Cmax was 481 ng/mL at 100 mg/kg in the TK study, indicating the exposure in this vivo study (highest dose was 100 mg/kg) might have exceeded (~1.5x) the high clinical exposure (the high clinical Cmax: 322 ng/mL). There were no RTA 408-related QTc, PR, QRS changes at tested doses. No positive drugs were used in the study.

In conclusion, while both in vitro hERG assay and in vivo study showed deviations from the best practice recommendations according to the new ICH S7B Q&As, results from the non-clinical data suggest that RTA408 could have a low risk for QT prolongation by direct inhibition of the hERG current at therapeutic exposure. However, the hERG assay and in vivo study may not be included in the integrated non-clinical risk assessment to support ICH E14 5.1 or 6.1.

4.2 APPLICANT'S RESULTS

4.2.1 By-Time Analysis

In the Applicant's by-time analysis, the largest mean of ΔQTcF was 3.7 msec for Omaveloxolone 150 mg (fasted) combining all Parts in Study 408-C-1806.

The primary analysis for Omaveloxolone was based on exposure-response analysis, please see section 4.2.3 for additional details.

Reviewer's comment: *FDA reviewer conducted the by-time analysis for Part 2 and Part 3 of Study 408-C-1806 separately. The largest ΔQTcF for Omaveloxolone 150 mg is 4.5 msec.*

4.2.1.1 Assay Sensitivity

Not applicable. Based on the nature of the evaluated clinical studies, it was not feasible to include placebo nor positive control, and therefore assay sensitivity was not established.

4.2.1.1.1 QT Bias Assessment

The Applicant analyzed data pooled from the food effect and DDI studies. The potential for Study induced QT bias was assessed by plots for conditional weighted residuals (CWRES) versus study. No other QT bias assessment was conducted by the Applicant.

Reviewer's comment: *To assess food induced QT bias, the Applicant conducted sensitivity analysis excluding data from fed conditions. In contrast to the Applicant's analyses, the reviewer completely excluded the food effect study from the analysis. In addition, like the Applicant, the reviewer excluded data from verapamil interaction part of the DDI study to avoid verapamil induced QT bias. However, in the reviewer's analysis, data from part 2 and 3 of the DDI study were analyzed separately.*

4.2.2 Categorical Analysis

There were no significant outliers per the Applicant's analysis for QTc (>500 msec). Results for HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline) were not available.

Reviewer's comment: *FDA reviewers conducted categorical analysis on QTc (>500 msec and >60 msec over baseline), HR (>100 beats/min and 25% over baseline), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline). No outlier was detected.*

4.2.3 Exposure-Response Analysis

The Applicant's primary analysis included pooled data from food effect and DDI studies. Data from the DDI study excluded part 4 of the study to avoid verapamil inducted QT bias. The Applicant states that pooling of the studies was justified since the ECGs were collected in the same manner and the PK samples used the same bioanalytical method. However, the Applicant also conducted a sensitivity analysis to evaluate the impact of the effect of pooling studies, the effect of food on QTc interval, and the effect of the co-administered enzyme inhibitors on QTc interval.

The Applicant used the model recommended in the white paper with modification to exclude treatment and time effect since the studies did not include placebo controls. According to the Applicant, the final model was to be selected from the sensitivity analyses if it was the most conservative, with reasonable goodness of fit plots, precision of estimates, and lower intra-individual variability (IIV) or residual variability. At the end, the Applicant selected the primary model from pooled data as the final model. The results of the Applicant's final model show an absence of significant QTc prolongation. The predicted mean (bias-corrected 90% CI) ΔQTcF at the Applicant's predicted steady state Cmax of 116 ng/mL (150 mg QD, fed) was -2.36 (-5.68, 0.582). The results from the Applicant's sensitivity analyses were consistent with the primary analysis.

Reviewer's comment: *In contrast to the Applicant's analysis, the reviewer excluded data from food effect study and analyzed from part 2 and part 2 of the DDI study separately. Despite this difference, the reviewer's findings support the Applicant's results that up to the maximum dose tested, omaveloxolone does not prolong the QTc interval.*

4.2.4 Safety Analysis

Study 408-C-1703

Overall, TEAEs were experienced by 1/10 (10.0%) subject in the 50 mg fasted group, 3 (37.5%) subjects in the 100 mg fasted group, 0/16 (0%) subject in the 150 mg group in a fasted state, and 1/15 (6.7%) subject in the 150 mg group in a fed state. All TEAEs were mild or moderate in severity. There were no deaths, SAEs, or AEs leading to withdrawal of study drug. One subject experienced a moderate presyncope in the 100 mg fasted group. The event was resolved and considered unrelated to the study drug by the investigator. No clinically relevant 12-lead ECG findings were identified for Part 1 or Part 2.

Study 408-C-1806

There were no deaths or SAEs during the study. Two subjects were withdrawn from the study due to TEAEs.

One subject in Part 1 experienced a TEAE of herpes zoster on Day 18 following administration of 2 single oral doses of 2 mg midazolam, 1 single dose of 1 mg repaglinide, 500 mg metformin, 10 mg rosuvastatin, and 0.25 mg digoxin, and 7 single doses of 150 mg omaveloxolone. Study treatment was permanently discontinued following dosing on Day 22 and early termination procedures were performed on Day 28. The TEAE was considered mild in severity and unlikely related to omaveloxolone or any of the probe drugs, by the investigator.

One subject in Part 3 experienced a TEAE of urinary retention on Day 11 following administration of a single oral dose of 150 mg omaveloxolone and 2 single oral doses of 200 mg itraconazole. Study treatment was permanently discontinued following onset of the AE and early termination procedures were performed on Day 23. The TEAE was considered moderate in severity and unrelated to omaveloxolone or itraconazole, by the investigator.

There were no severe TEAEs reported during the study. The majority of TEAEs were mild in severity, with only 3 moderate TEAEs reported in 2 subjects.

During all parts of the study, there were no clinically significant changes in the 12-lead ECG parameters for individual subjects. The mean ECG parameters following omaveloxolone dosing alone and omaveloxolone co-administered with probe drugs were comparable in all study parts.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., unexplained syncope seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred. QT prolongation-related safety analysis was further performed on Study 408-C-1402 Part 2,* (b) (4) *as it provides a placebo comparison and utilized the proposed marketed dose and formulation. See Section 5.6.*

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 5.3.2).

5.2 ECG ASSESSMENTS

5.2.1 Overall Quality

Paper ECGs were submitted. Automatic measurements were also available for analyses. Overall, ECG acquisition and interpretation in this study appear acceptable.

5.2.2 QT Bias Assessment

Not applicable as only automated QTc readings from paper ECGs were available for data included in the analysis.

5.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer evaluated the ΔQTcF effect using descriptive parametric statistics.

5.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups. The maximum ΔQTcF values by treatment are shown in Table 3.

Figure 1: Mean and 90% CI of ΔQTcF Time-course (unadjusted CIs).

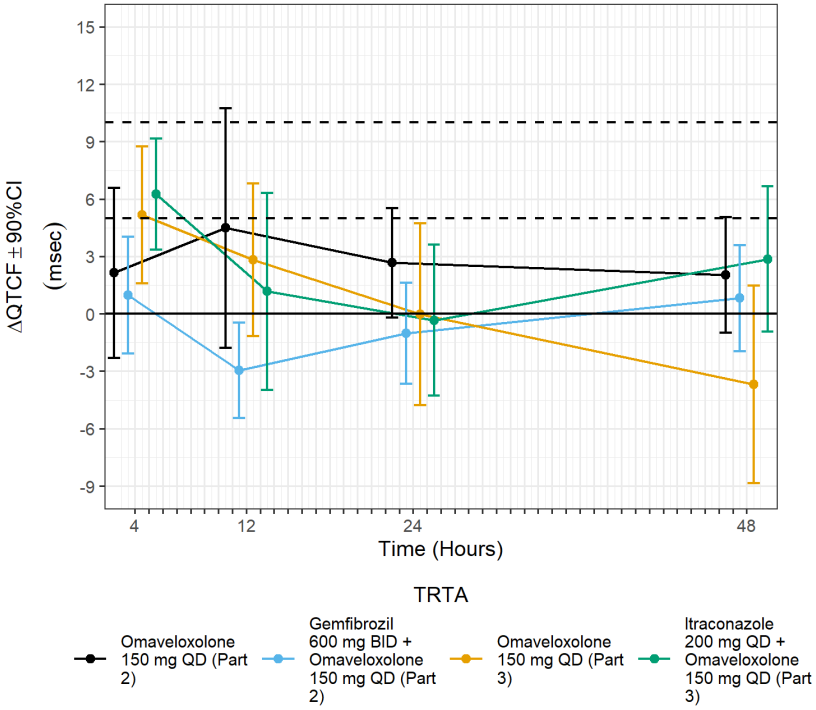


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Actual Treatment	N	Time (Hours)	ΔQTCF (msec)	90.0% CI (msec)
Omaveloxolone 150 mg QD (Part 2)	15	12.0	4.5	(-1.8 to 10.8)
Gemfibrozil 600 mg BID + Omaveloxolone 150 mg QD (Part 2)	14	4.0	1.0	(-2.1 to 4.0)
Omaveloxolone 150 mg QD (Part 3)	15	4.0	5.2	(1.6 to 8.8)
Itraconazole 200 mg QD + Omaveloxolone 150 mg QD (Part 3)	14	4.0	6.3	(3.4 to 9.2)

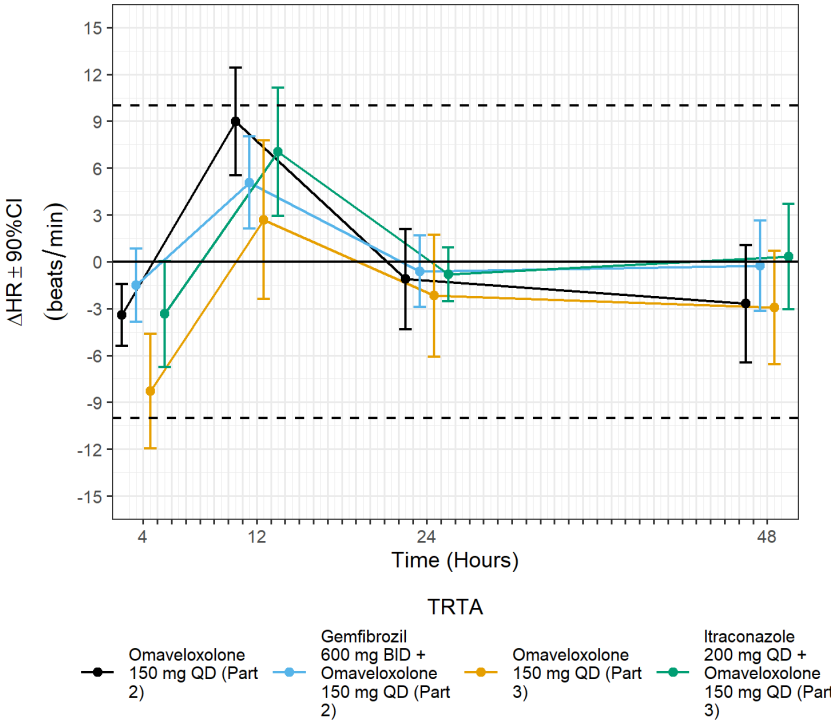
5.3.1.1 Assay Sensitivity

Not applicable.

5.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups.

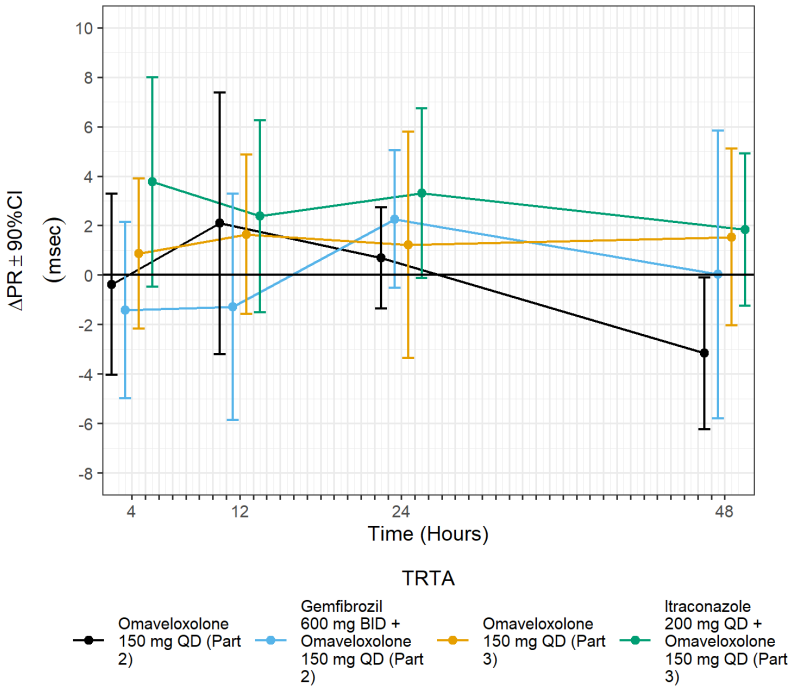
Figure 2: Mean and 90% CI of ΔHR Time-course



5.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups.

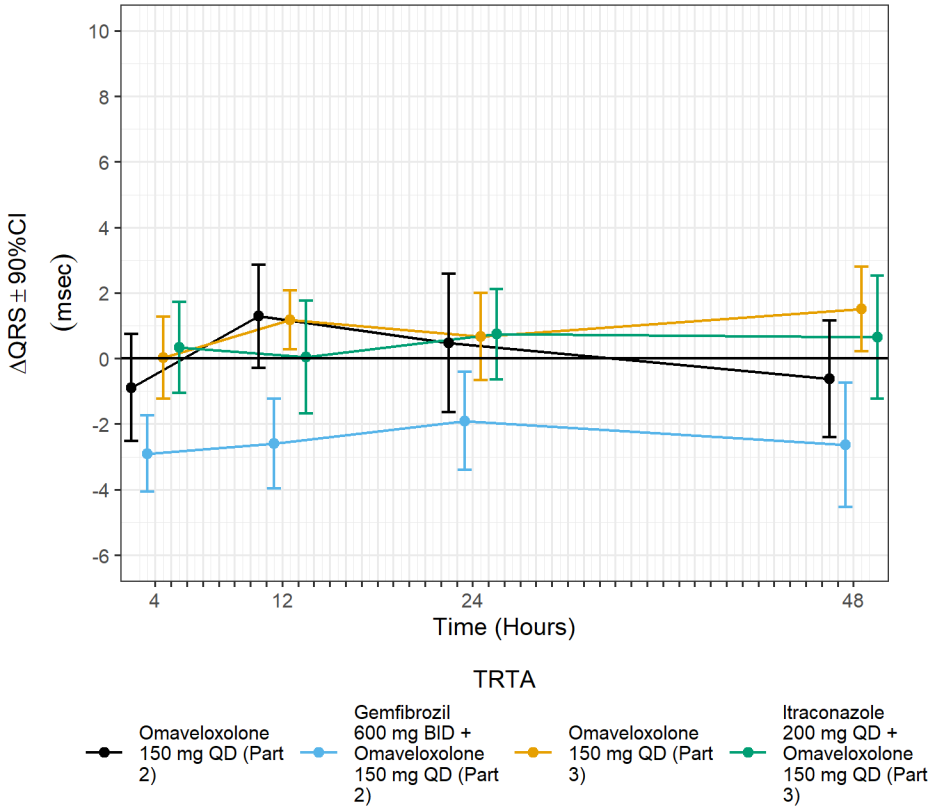
Figure 3: Mean and 90% CI of ΔPR Time-course



5.3.4 QRS

Figure 4 displays the time profile of ΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔQRS Time-course



5.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

5.4.1 QTc

None of the subjects had QTcF value >500 msec. None of the subjects had ΔQTcF value >60 msec.

5.4.2 HR

None of the subjects had HR>100 beats/min.

5.4.3 PR

None of the subjects had PR value >220 msec and 25% over baseline.

5.4.4 QRS

None of the subjects had QRS value >120 msec and 25% over baseline.

5.5 EXPOSURE-RESPONSE ANALYSIS

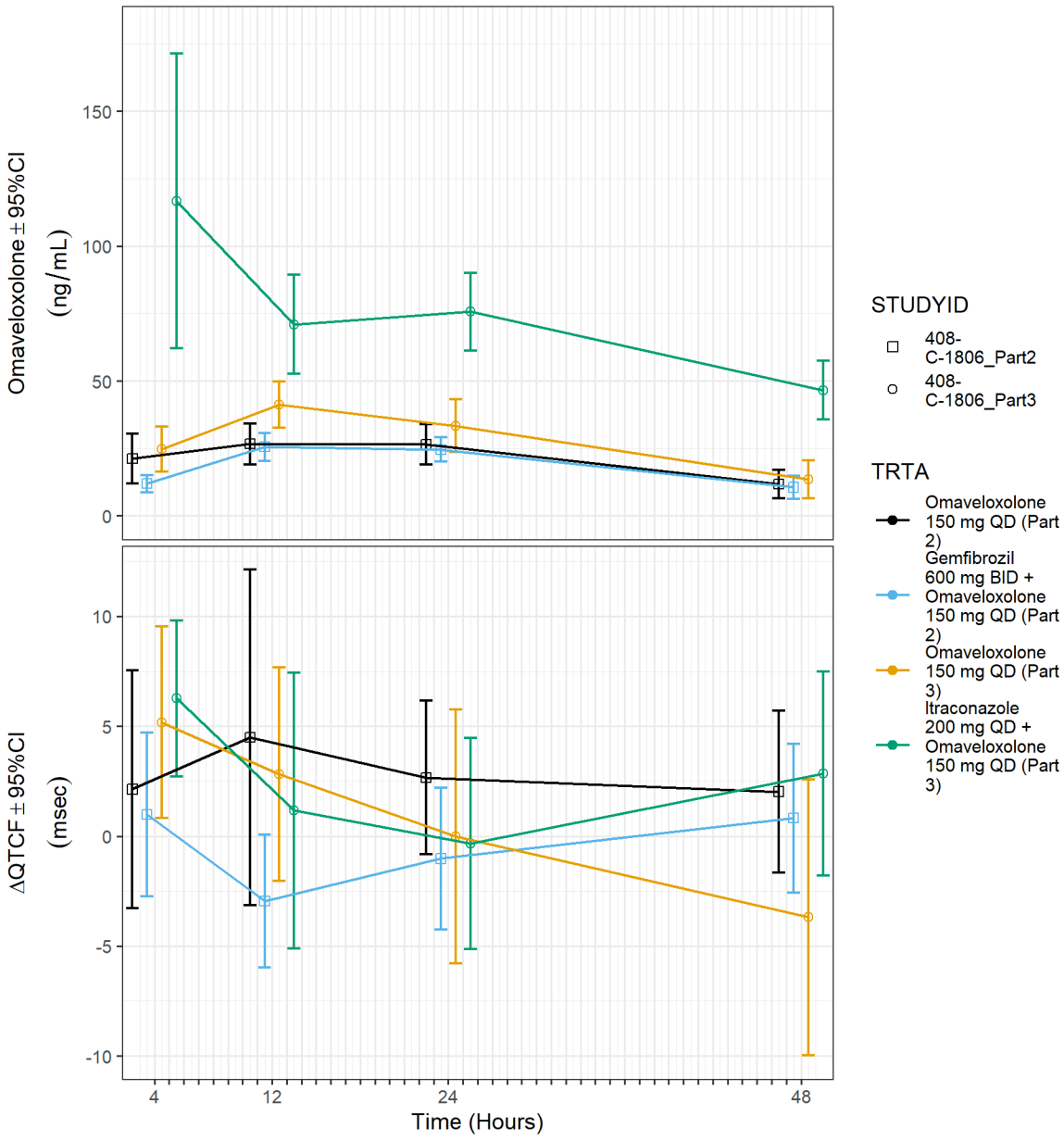
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. Data from part 2 (n=15) and part 3 (n = 15) of the DDI study were analyzed separately.

5.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔQTcF; and 3) absence of a nonlinear relationship.

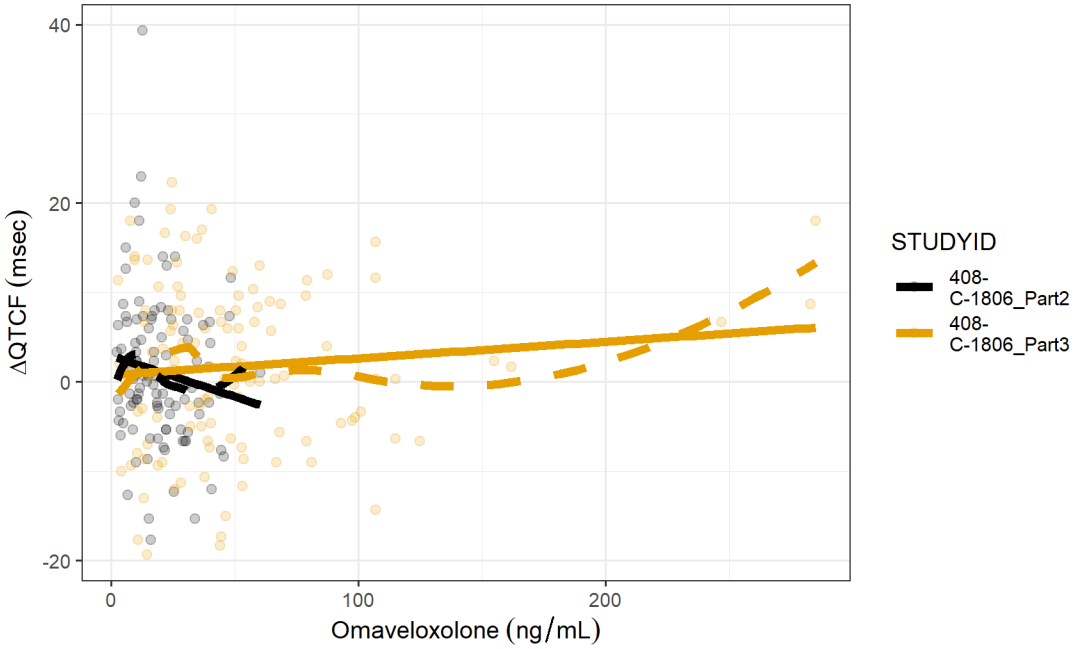
Figure 2 shows the time-course of ΔHR, with an absence of significant ΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔQTcF, with no appearance of significant hysteresis. It should be noted however that the interval between ECGs is > 6 hour. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



[1] ΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 5.

Figure 7: Goodness-of-fit Plot for QTcF for Part 2 of study 408-C-1806

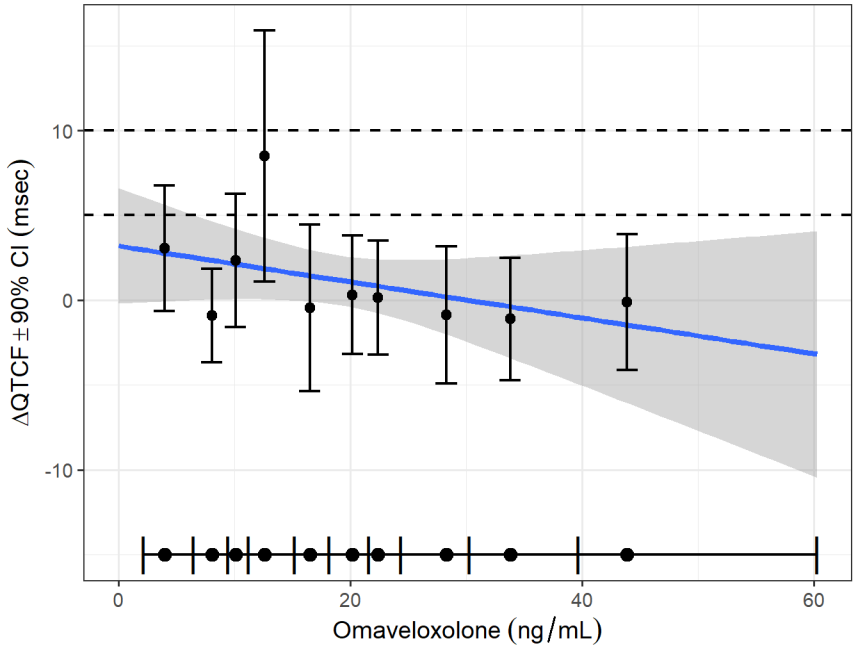


Figure 8: Goodness-of-fit Plot for QTcF for Part 3 of study 408-C-1806

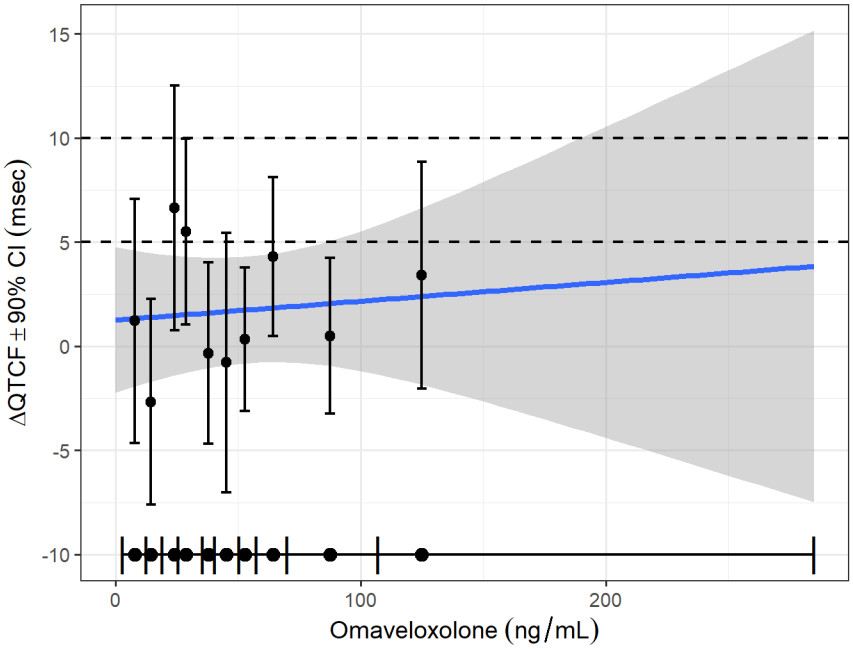


Table 4: Predictions from Concentration-QTcF Model Part 2 of study 408-C-1806

Actual Treatment	Analysis Nominal Period Day (C)	Omaveloxolone (ng/mL)	ΔQTCF (msec)	90.0% CI (msec)
Gemf brozil 600 mg BID + Omaveloxolone 150 mg (Part 2)	1	28.2	0.2	(-2.0 to 2.4)
Omaveloxolone 150 mg (Part 2)	1	29.7	0.0	(-2.4 to 2.5)

Table 5: Predictions from Concentration-QTcF Model Part 3 of study 408-C-1806

Actual Treatment	Analysis Nominal Period Day (C)	Omaveloxolone (ng/mL)	ΔQTCF (msec)	90.0% CI (msec)
Omaveloxolone 150 mg (Part 3)	1	39.7	1.6	(-1.0 to 4.3)
Itraconazole 200 mg + Omaveloxolone 150 mg (Part 3)	1	110.4	2.3	(-1.4 to 6.0)

5.5.1.1 Assay Sensitivity

Not applicable. The study did not include placebo nor positive control for assessment of assay sensitivity.

5.6 SAFETY ASSESSMENTS

Study 408-C-1402 Part 2 was a randomized, placebo-controlled, double-blind, parallel-group study to evaluate the safety and efficacy of omaveloxolone 150 mg in patients with FA. 51/52 patients received at least one dose of omaveloxolone/placebo. Following randomization on Day 1, patients self-administered study treatment once daily for 48 weeks. A follow-up visit for safety occurred at Week 52 (4 weeks after the last dose). ECGs were performed at screening, week 2, 4, 12, 18, 24, 36, 48 (end of treatment), and 52 (end of study).

There were no deaths in the study. SAEs were reported for 5 patients (9.8%) in the omaveloxolone group (atrial fibrillation, laryngitis, viral upper respiratory tract infection (URTI), palpitations, noncardiac chest pain, sinus tachycardia, anemia, ventricular tachycardia, and craniocerebral injury) and 3 patients (5.8%) in the placebo group (gallbladder disorder, ankle fracture, and atrial fibrillation).

Ventricular tachycardia:

Subject (b) (6) *was a 30-year-old, white, non-Hispanic or Latino female patient. She was diagnosed with FA at 11 years of age. She received omaveloxolone 150 mg from* (b) (6) *until* (b) (6)*. On Study Day 29* (b) (6) *the patient experienced the SAE of ventricular tachycardia. The last dose of study drug prior to the event was administered on Study Day 17* (b) (6)

On (b) (6)*, baseline transthoracic echocardiography showed no abnormality. A baseline ECG revealed low voltage and diffuse repolarization abnormalities; however, they were not considered clinically significant. Baseline liver function tests were within normal limits.*

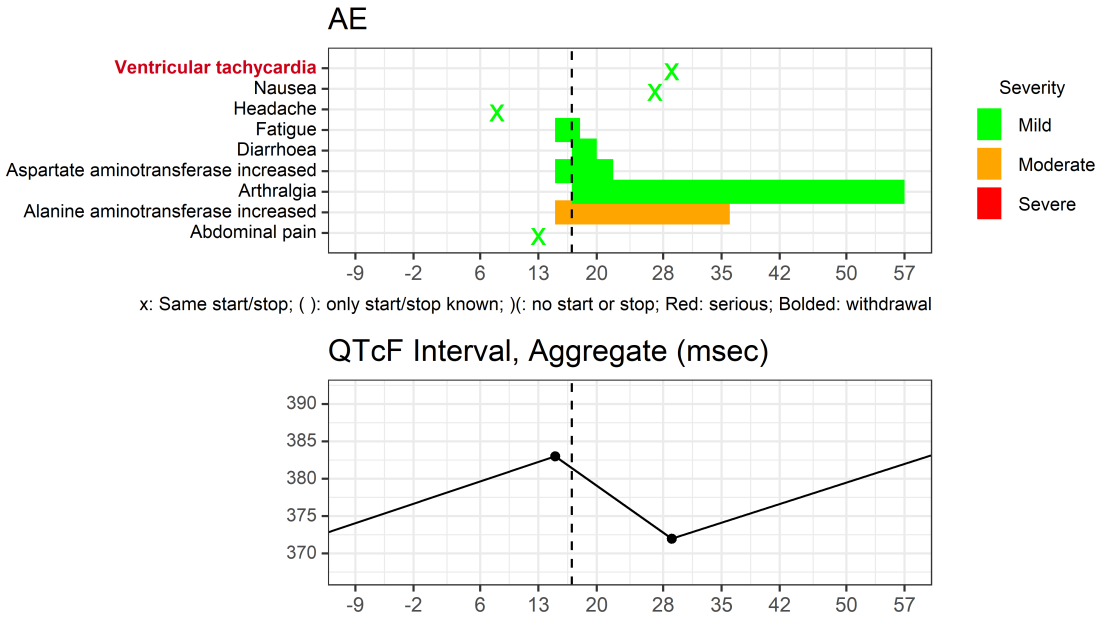
On Study Day 15 (b) (6)*, laboratory testing revealed an elevated ALT of 132 U/L, an elevated AST of 69 U/L, TBL of 4 μmol/L, lactate dehydrogenase of 174 U/L, and GGT of 11 U/L. On the same day, ECG results revealed no clinically significant abnormalities. On Study Day 17* (b) (6) *laboratory testing revealed an ALT of 170 U/L, AST of 85 U/L, TBL of 5 μmol/L, lactate dehydrogenase of 222 U/L, and GGT of 13 U/L, and the study drug was interrupted on the same day. Elevated liver enzymes were reported as a nonserious AE, and transaminase levels returned to within normal limits on Study Day 29* (b) (6) *[ALT of 28 U/L; AST of 23 U/L].*

On Study Day 29 (b) (6) *12 days after discontinuation of study drug, a week-4 exercise test revealed trace ventricular tachycardia of 175 beats per minute (resting rate, 90 beats per minute) at peak exercise. The patient remained asymptomatic and had a normal recovery without treatment, and the event of ventricular tachycardia was considered resolved on the same day. The patient was evaluated by a cardiologist on Study Day 50* (b) (6) *and an ECG revealed sinus rhythm, a normal QTc interval, and widespread repolarization abnormalities. An ECG revealed low to normal left ventricular ejection fraction but was otherwise unremarkable. The patient underwent a 24-hour Holter monitor analysis; results were unremarkable and showed sinus rhythm throughout with a maximum heart rate of 113 beats per minute. The cardiologist concluded that the findings suggest a mild FA cardiac phenotype, and a low-dose β-blocker was recommended.*

On Study Day 57 [redacted] (b) (6) *, cardiac magnetic resonance imaging revealed normal right and left ventricle volumes, an aberrant origin of the right subclavian artery with retro-esophageal course to right, suspicion of subepicardial fibrosis in the left ventricle lateral wall, and no left ventricular hypertrophy or myocardial inflammation, edema, or infarction. This new information was evaluated by the cardiologist, who then considered the event of nonsustained ventricular tachycardia to be out of keeping with the phenotype and unexpected and therefore recommended the patient not re-start the study medication. The study drug was not restarted and was permanently discontinued due to the SAE.*

The Investigator considered the event of ventricular tachycardia serious, mild in intensity, and unlikely related to the study drug. The Investigator identified a possible cause of the event as underlying cardiac disease. The event occurred 12 days after the discontinuation of study drug (CSR p2603). Figure 9 showed the narrative plot for this patient.

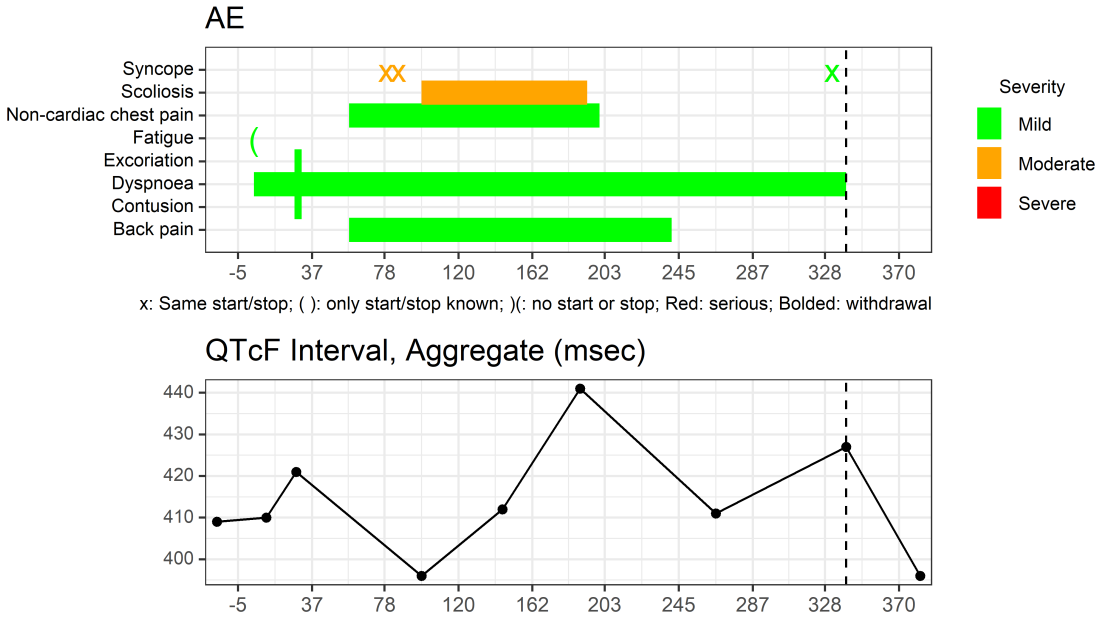
Figure 9. Narrative for Subject [redacted] (b) (6) .



Four patients (7.8%) in the omaveloxolone group (PT: AST increased, ALT increased, muscle spasms, ventricular tachycardia [SAE], and rosacea) and 2 patients (3.8%) in the placebo group (PT: atrial fibrillation [SAE] and erythrosis) permanently discontinued study drug because of a TEAE.

MedDRA SMQ (version 14.0) of "Torsade de pointes/QT prolongation" (broad) plus PT "Seizure" showed 2 subjects in the omaveloxolone group had related TEAEs. One subject [redacted] (b) (6) had two moderate syncope episodes (Day 79 and 86) and one mild syncope episode (Day 332). QTcF was within normal range (Figure 10). The events were resolved on the same day and was considered not related to study treatment. One subject [redacted] (b) (6) had an SAE of ventricular tachycardia that led to discontinuation of treatment (Figure 9 and narrative above). No subjects in the placebo group had any torsade de pointes-related event.

Figure 10. Narrative for Subject (b) (6).



Reviewer's comments: For subject (b) (6)*, the ventricular tachycardia occurred almost two weeks after the discontinuation of omaveloxolone and unlikely to be related to the treatment. For subject* (b) (6)*, QTcF around the syncope episodes appeared to be within normal range.*

6 APPENDIX

6.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

1. Product Information			
Generic Name	omaveloxolone	Brand Name	Skyclarys
Drug Class	Nrf2 activator		
Combination Product	No		
Indication	Friedreich's ataxia		
Therapeutic Dose	150 mg once daily on empty stomach		
Maximum Tolerated Dose	None		
Dosage Form	Immediate release capsules	Route of Administration	oral

2. QT Studies								
2.1 Primary Studies								
Protocol Number / Population	**ECG Quality**		**Arms**		**Sample Size**		**ECG & PK Assessments**	
	Assessment	**OK?**	**Arms**	**High Dose Covers?**	**No Subjects**	**OK?**	**Timing**	**OK?**
Protocol Number: Study 408-C1703, Study 408-C1806	Central Read? No Blinded? No Replicates? Yes	Yes	Highest Dose: 150 mg Placebo: No Positive Control: No	Therapeutic	15	Yes	Baseline: Pre-dose baseline Timing: Study 408-C1703: ECGs collection at Pre-dose and at 3 and 24 h post dos; Study 408-C1806:	*No*

Population: Healthy volunteers Design: Crossover							ECGs collection at pre-dose, 4, 12, 24, and 48 h post dose on Day 1 and Day 13	

In Study 408-C1703 (food effect study), median Tmax after 50-, 100-, and 150-mg under fasted condition were 5.5-, 10-, and 11-h respectively. Under fed condition median Tmax after 150 mg dose was 5 (2, 8) hours.

The median (range) Tmax in part 2 of DDI study after omaveloxolone alone and with gemfibrozil were 14.29 (1.00-24.43) and 11.95 (2.00-34.02) hours, respectively. The median (range) Tmax in part 3 after omaveloxolone alone and with itraconazole were 12.00 (2.00-24.00) and 6.00 (2.00-36.00) hours, respectively.

The ECGs collection schedule in both food effect and DDI studies is very sparse and may not have characterized QT effects at Cmax for some individuals.

2.2 Secondary Studies

NA.

2.3 Data Pooling

Data pooling?	Yes
Did sponsor propose an assessment for heterogeneity?	No
Is the data pooling appropriate?	No

The sponsor proposed to pool food effect and DDI studies. The sponsor's justification for data pooling is that ECG collection methods and PK bioanalysis methods were similar between the two studies. However, the differences in the study designs between the two studies do not support pooling of the two studies. For example, while food is known to shorten QT interval, the DDI study was conducted under fasting conditions in contrast to the food effect study; furthermore, unlike the DDI study, the food effect study did not capture ECGs at around Tmax of omaveloxolone.

3. Analysis plan

3.1 Study Objectives Related to QT

What QTc effect size is the analysis trying to exclude?	10 ms (E14)
3.2 Dose Justification	
The anticipated high clinical exposure scenario is when omaveloxolone 150 mg is inadvertently co-administered with food at the steady state of dosing. The maximum dose tested does not covers the therapeutic exposure but not the high exposure scenario.	
3.3 QT Correction Method	
Is an HR increase or decrease greater than 10 beats/min?	No
Primary method for QT correction	QTcF
3.4 Assay Sensitivity	
Assay sensitivity methods proposed by sponsor	☐ Moxifloxacin ☐ Exposure-margin ☐ QT bias assessment ☐ Other ☒ Not applicable (objective is large mean effects)
3.5 By-Time Analysis	
3.5.1 Investigational Drug	
Primary analysis	No
Did the sponsor use IUT or descriptive statistics?	Descriptive statistics
For IUT: Does the sponsor use MMRM to analyze longitudinal values that consider the correlation across time-points, or use ANCOVA by-time-point without considering correlation?	N/A
For IUT: Is the MMRM model specified correctly with regard to covariance structure, covariates, or if ANCOVA, is the model specified correctly with regard to covariates?	N/A
Summary statistics of ΔQTcF by study and timepoint are presented.	
3.5.2 Positive Control	
Primary analysis	N/A

Did the sponsor adjust for multiplicity?	N/A
N/A.	

3.6 Exposure-Response Analysis	
3.6.1 Investigational Drug	
Primary analysis	Yes
What is the dependent variable in the sponsor's model?	Single delta
White paper model?	Yes
Which concentration covariate(s) are included in the model?	Parent
Did the sponsor propose an assessment of delayed effects?	Yes
Did the sponsor propose an assessment of linearity?	Yes
Did the sponsor propose model selection criteria?	Yes
Which methods did the sponsor use for predicting the QT effect?	☐ Model-based confidence intervals ☒ Bootstrap-derived confidence intervals
3.6.2 Positive Control	
Primary analysis	N/A
Same model as investigational drug	N/A
The study did not include positive control	

3.7 Categorical Analysis			
QTcF?	Yes	QRS?	Yes
ΔQTcF?	Yes	HR?	Yes
PR?	Yes	T-wave morphology?	Unknown

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/s/

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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 8, 2022

To: Teresa Buracchio, MD, Director
Division of Neurology 1 (DN1)

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Edward Hawkins, PhD, Pharmacologist
Controlled Substance Staff

Subject: **Product name:** SKYCLARYS **(**omaveloxolone, RTA408)
Dosages, formulations, routes: 50 mg oral tablets; max daily dose of 150 mg
NDA number: 216718
IND Number: 122349
Indication(s): treatment of Friedreich's ataxia
PDUFA Goal Date: November 20, 2022

Materials Reviewed:

- NDA 216718 for SKYCLARYS **(**omaveloxolone, RTA408), submitted as two parts
  - Part 1 submitted January 28, 2022
  - Part 2 submitted March 30, 2022
- IND 122349 for omaveloxolone
  - DARRTS; IND 122349; Hawkins, Edward; 8/20/2021; consult review

Table of Contents

I. SUMMARY

1. Background

This memorandum is in response to a consult request from the Division of Neurology 1 (DN1) to evaluate abuse-related preclinical and clinical data submitted by Reata Pharmaceuticals, Inc. (Applicant) under NDA 216718 and IND 122349 for SKYCLARYS (omaveloxolone, RTA408). The Applicant submitted a 505(b)(1) application, and DN1 consulted CSS to review the abuse-related data submitted as part of the NDA. Omaveloxolone was granted orphan drug designation (14-4612) on June 19, 2017, and Fast Track Designation on November 17, 2021. The request for Rare Pediatric Disease Designation is currently under review by The Office of Orphan Products Development (OOPD). An Advisory Committee (AC) meeting has tentatively been scheduled for October 4, 2022, to discuss the drug product.

Omaveloxolone is an orally bioavailable nuclear factor, erythroid 2-like 2 (Nrf2) activator and is being proposed for the treatment of Friedreich's ataxia. Omaveloxolone is formulated as a capsule of 50 mg to be taken three times a day.

After evaluating the nonclinical and clinical data in the NDA, CSS recommends that omaveloxolone not be controlled under any schedule of the Controlled Substances Act (CSA).

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 216718 for omaveloxolone and concludes that the drug does not have abuse potential and should not be controlled under the CSA. This conclusion is based on the following:

- Omaveloxolone is a new molecular entity whose primary mechanism of action is as an activator of Nrf2. Receptor binding studies indicated that omaveloxolone did not bind to any receptors, transporters, or ion channels typically associated with drugs having a potential for abuse.

- Omaveloxolone is metabolized into two major circulating metabolites M17 and M22. The Sponsor did not conduct receptor binding studies on these metabolites.

- In animal behavior and toxicity studies, omaveloxolone did not produce any central nervous system (CNS)-mediated effects or behaviors.

- The Applicant did not conduct animal abuse potential studies such as a self-administration, drug discrimination, or physical dependence studies.

- The Applicant did not conduct a human abuse potential study.

- An analysis of CNS-mediated adverse events (AEs) that can be indicative of abuse liability was conducted on the clinical studies provided by the Applicant. This analysis indicated that the most prevalent AEs were headache and nausea. There were no reports of AEs that suggest that omaveloxolone has a potential for abuse.

3. Recommendations

Based on the data provided in NDA (b) (4), CSS recommends that:

- Omaveloxolone not be controlled in any schedule under the CSA

- Section 9: DRUG ABUSE AND DEPENDENCE should not appear in the label

II. DISCUSSION

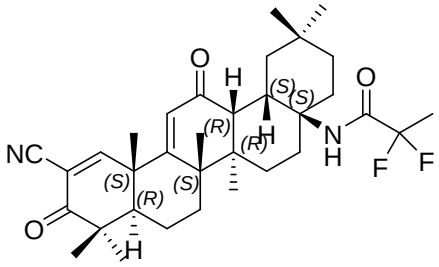
1. Chemistry

1.1 Substance and Product Information

Omaveloxolone is the name of the active pharmaceutical ingredient in SKYCLARYS. SKYCLARYS is formulated as a 50 mg capsule for oral consumption. Omaveloxolone, also known by the developmental codes RTA408 or TX-0063415 is the nonproprietary name of N-(2-Cyano-3,12-dioxo-28-noroleana-1,9(11)-dien-17-yl)-2,2-difluoropropanamide. Omaveloxolone has a molecular mass of 554.72 g/mol, a chemical formula of $C_{33}H_{44}F_2N_2O_3$, and a CAS # of 1474034-05-3. The drug substance is a white to off-white powder that is freely soluble in acetone and sparingly soluble in ethanol (APPEARS THIS WAY ON ORIGINAL

Table **1**). Omaveloxolone is not currently listed in any schedule of the CSA.

Table 1: General Chemical Properties of Omaveloxolone

Nomenclature	
International Non-proprietary Name (INN)	Omaveloxolone
Chemical Abstract Number (CAS)	1474034-05-3
Chemical Name (IUPAC)	N-(2-Cyano-3,12-dioxo-28-noroleana-1,9(11)-dien-17-yl)-2,2-difluoropropanamide
Drug product codes	RTA408, TX-0063415
Schedule in the CSA	not controlled
Structure	
Molecular Formula	$C_{33}H_{44}F_2N_2O_3$
molar mass	554.72 g mol^{-1}
Structure	
General Properties	
Appearance	White to off-white
pKa	7.62
Solubility (25°C)	soluble in acetone, slightly soluble in ethanol, insoluble in water
Chiral form	Seven chiral centers

Excipients in the tablet

The total capsule weight for the 50 mg dose capsule is 400 mg (b) (4) . There are no excipients in the 50 mg tablet that present concerns from an abuse liability perspective.

1.2 In Vitro Manipulation and Extraction Studies for Products with Abuse-Deterrent Features

The Applicant is not seeking abuse-deterrent labeling and did not conduct manipulation or extraction studies to assess the abuse-deterrent properties of omaveloxolone.

2. Nonclinical Pharmacology

2.1 Receptor Binding and Functional Assays

The Applicant conducted several in vitro binding studies to assess the primary and secondary pharmacology of omaveloxolone. These studies determined that omaveloxolone is a novel, potent, orally bioavailable nuclear factor, erythroid 2-like 2 (Nrf2) activator. It reversibly binds to Kelch-like ECH-associated protein 1 (Keap1), resulting in the activation of Nrf2, a transcription factor that modulates the expression of genes involved in regulating mitochondrial function, oxidative stress, and inflammation.

Study # RTA-P-18007 – was a (b) (4) binding study conducted to determine the binding activity of omaveloxolone at 200 nM and at 2000 nM against receptors, ion channels, and transporters associated with abuse potential. In these studies, percent inhibition of control specific binding of 50% is typically considered significant and requiring further evaluation (i.e., functional characterization). CSS typically recommends that these studies be conducted at a drug concentration of 10,000 nM (10 µM). In this study, omaveloxolone did not bind to any molecular targets typically associated with having a potential for abuse at the higher concentration. It is unlikely the drug will reach a concentration of 2000 nM (2 µM) in the central nervous system as concentrations of 200 and 2000 nM correspond to approximately 50- and 500-fold the free drug C_{max} (~3.75 ng/mL) in subjects who received 150 mg omaveloxolone (phase 1 study #s 408-C-1805 and 408-C-1804).

Metabolites

The Sponsor identified three metabolites in Study # 408-C-1805 in which healthy subjects received single oral doses of 150 mg [^{14}C]-omaveloxolone. The metabolites were 1,2-dihydro-29-OH omaveloxolone (M17 (10.9% of parent)), 1,2-dihydro-30-COOH omaveloxolone (M22 (18.6% of parent)), and 1,2-epoxy omaveloxolone (M29 (35.9% of parent)). M17 and M22 were detected in plasma and M29 was detected in the feces. The metabolites were not assessed in in vitro binding studies. Notably, 40.3% of unmetabolized omaveloxolone was detected in the feces.

Conclusion

Omaveloxolone is an activator of nuclear factor, erythroid 2-like 2 (Nrf2). Omaveloxone does not bind to molecular targets typically associated with having a potential for abuse at the concentrations tested in the study.

2.2 Findings from Safety Pharmacology and Toxicology Studies

The Applicant conducted a series of animal safety studies to assess the pharmacology and pharmacokinetics (PK) of omaveloxolone. The review will only focus on CNS mediated studies and behaviors.

CNS mediated behaviors

Study # RTA408-P-1115 – was a functional observational battery (FOB) in which rats received single oral doses of 0, 3, 10, or 30 mg/kg omaveloxolone. Rats were observed in behavioral assessments pre-dose and up to 24 hours post dose. No consistent behavioral effects were observed during the study. A

slight decrease in body weight was noted after 24 hours in the 30 mg/kg test group, however, it is unclear if this was drug related.

2.3 Animal Behavioral Studies

Toxicity Studies

The Sponsor conducted 13 repeat dose toxicity studies in mice, rats, monkeys, and minipigs. Several of the studies were conducted to determine the toxicity of dermal or ocular administration of the drug, however, these will not be reviewed here because the Sponsor is seeking approval for an oral dosage formulation. Rats were found to be more sensitive than other species to the toxic effects of omaveloxolone with the Sponsor reporting a NOAEL of 3 mg/kg/day for 28-days of administration. At higher doses, rats demonstrated adverse effects to the liver and kidney some of which dissipated after discontinuation of drug administration. There were indications of increased organ weight, including the brain, however, there were no obvious treatment emergent CNS-mediated behaviors reported in the toxicity studies.

Animal Abuse Potential Studies

The Sponsor did not conduct animal abuse potential studies.

2.4 Tolerance and Physical Dependence Studies in Animals

No animal studies were conducted by the applicant to assess the tolerance or physical dependence of omaveloxolone.

3. Clinical Studies

3.1 Human Abuse Potential Studies

The Applicant was not required to conduct a human abuse potential study to assess the abuse liability of omaveloxolone.

3.2 Adverse Event Profile Through all Phases of Development

Adverse Events in Clinical Studies Conducted by the Applicant

The Applicant conducted 10 clinical studies to assess the safety, pharmacokinetics, bioavailability, and efficacy of omaveloxolone. All AEs, including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). The following is a description and analysis of abuse-related AEs found during these studies.

Four of the studies were conducted in healthy adult subjects with the other six studies being conducted in subjects who were clinically diagnosed with Friedreich's ataxia. Subjects received doses ranging from 5 to 300 mg with the highest therapeutic dose of 50 mg TID. Subjects with Friedreich's ataxia may be

neurologically impaired and therefore adverse events relating to abuse may not be drug related in that subject population.

There were no reports of treatment emergent adverse events that are strongly associated with abuse potential (i.e., euphoric mood, hallucinations, etc.) in any of the studies, including for healthy subjects in phase 1 studies. There were no AEs reported that indicate that omaveloxolone produces a potential for abuse at the doses tested. The highest CNS-related AEs reported (# (%)) were headache 19 (37.3%) and nausea 23 (45.1%).

3.4 Evidence of Abuse, Misuse, and Diversion in Clinical Trials

There were no reports of misuse, abuse, or diversion of omaveloxolone in clinical trials.

4. Regulatory Issues and Assessment

There are no regulatory issues regarding the abuse potential of omaveloxolone. Omaveloxolone does not have abuse potential and will not be required to be controlled under the CSA.

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/s/

EDWARD G HAWKINS
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DOMINIC CHIAPPERINO
08/18/2022 08:47:16 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 29, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216718
Product Name and Strength:	Skyclarys (omaveloxolone) capsule, 50 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Reata Pharmaceuticals, Inc.
FDA Received Date:	January 28, 2022; May 6, 2022; June 15, 2022
OSE RCM #:	2022-304
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Skyclarys (omaveloxolone) capsule, the Division of Neurology 1 (DN 1) requested that we review the proposed Skyclarys prescribing information (PI), patient prescribing information (PPI), and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed PI, PPI, and container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Reata Pharmaceuticals, Inc.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	Under Indications and Usage, (b) (4)	(b) (4) may be a source of confusion.	We recommend (b) (4)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	Under Dosage and Administration, the instructions for taking the product in relation to food (b) (4)	Unclear instructions may lead to improper administration of the drug.	We recommend combining the two food-related administration statements for clarity. Revise to read: "(b) (4) on an empty stomach at least 1 hour before eating" or similar.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The recommended dosage statements are excessively wordy.	Unclear dosage information may lead to dosing errors.	We recommend combining the recommended dosage statements for simplicity. Revise to read "The recommended dosage of SKYCLARYS is 150 mg (3 capsules) taken orally once daily" or similar.
2.	The food-related administration statements are in separate bullet points and do not align with the statements in the HPI.	Unclear instructions may lead to improper administration of the drug.	We recommend combining the food-related administration statements as recommended for the HPI to align between sections.
3.	Under (b) (4) the statement (b) (4) is ambiguous.	Unclear instructions may lead to dosing errors.	We recommend clarifying that (b) (4) means not to use SKYCLARYS if that is the intent. Additionally, we recommend clarifying this statement in Table 1 (b) (4) .
Full Prescribing Information – Section 17 Patient Counseling			
1.	Food-related administration instructions are missing.	Incomplete patient instructions may lead to improper administration of the drug.	For completeness, we recommend adding food-related administration language to align with the HPI and Section 2.
Patient Prescribing Information (PPI)			

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The statement "Your healthcare provider may change your dose during treatment, stop treatment for some time, or completely stop treatment with SKYCLARYS (b) (4) appears inaccurate.	This does not align with the information presented in the proposed PI.	It does not appear there are any recommended dosing modifications at the time of this review, so we recommend removing the statement "change your dose during treatment" to align with the PI.
2.	The food-related administration statement is missing important information.	Incomplete instructions may lead to improper administration of the drug.	We recommend revising the food-related administration language to align with the HPI, Section 2, and Section 17.

5 RECOMMENDATIONS FOR REATA PHARMACEUTICALS, INC.

Table 3. Identified Issues and Recommendations for Reata Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The dosage form statement is presented after the strength statement, and not immediately following the established name.	This is not in alignment with our Guidance document Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors available from: https://www.fda.gov/media/158522/download	We recommend moving the dosage form statement to appear either on the same line as the established name or directly below the established name.
2.	The recommended dosage statements include numbers (150 mg and 3 capsules) and clutter the principal display panel (PDP).	This can be improved for readability and to reduce the risk for confusion with other numbers on the PDP, such as the strength of the product or net quantity.	We recommend relocating the recommended dosage statements to the side panel. See also recommendation #3 below.

Table 3. Identified Issues and Recommendations for Reata Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The recommended dosage statements suggest there may be more than one dosage regimen, whereas only one regimen is described in the prescribing information.	The current statements can be improved for clarity and brevity.	We recommend revising the statements, (b) (4) to read "Recommended Dosage: Take 150 mg (3 capsules) orally once daily." Alternatively, you may choose to (b) (4)
4.	The manufacturer information is more prominent than the strength statement.	This is not in alignment with 21 CFR 201.15(a)(6). Further, the product strength is critical information that should be easily identifiable on the label.	We recommend increasing the prominence of the strength statement in relation to the manufacturer information.
5.	The product identifier, which includes the lot number and expiration date, is not present.	This is not in alignment with The Drug Supply Chain Security Act (DSCSA). The guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf	In June 2021, FDA finalized a guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling.
6.	The format for the expiration date is not defined.	We are unable to assess from a medication error perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.

Table 3. Identified Issues and Recommendations for Reata Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Skyclarys that Reata Pharmaceuticals, Inc. submitted on June 15, 2022.

Table 4. Relevant Product Information for Skyclarys	
Initial Approval Date	n/a
Active Ingredient	Omaveloxolone
Indication	Treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older
Route of Administration	Oral
Dosage Form	Capsule
Strength	50 mg
Dose and Frequency	150 mg (3 capsules) once daily
How Supplied	Bottles containing 90 capsules
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure[a]	HDPE bottle with foil seal and (b) (4) child-resistant closure

[a] Container closure specifications available at: \\CDSESUB1\evsprod\nda216718\0003\m3\32-body-data\32p-drug-prod\omaveloxolone-capsules-capsule-hard\32p7-cont-closure-sys\container-closure-system-1.pdf

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 16, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, omaveloxolone, NDA 216718, and IND 122349. Our search did not identify any previous labels and labeling reviews for this product.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Skyclarys labels and labeling submitted by Reata Pharmaceuticals, Inc.

- Container label, received on January 28, 2022
- Patient Prescribing Information (image not shown), received on May 6, 2022, available from: \\CDSESUB1\evsprod\nda216718\0005\m1\us\114-labeling\final\package\patient-informationdocx.docx
- Prescribing Information (Image not shown), received on June 15, 2022, available from: \\CDSESUB1\evsprod\nda216718\0011\m1\us\114-labeling\draft\labeling\day-60-draft-labelling-text-uspi-clean.docx

F.2 Label and Labeling Images

Container label

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JOHN C MORRIS
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STEPHANIE L DEGRAW
07/29/2022 11:59:07 AM

Memorandum

From: Selena DeConti, PharmD, MPH
Safety Analyst, Division of Cardiology and Nephrology
Office of New Drugs/CDER/FDA

Through: Mary Ross Southworth, PharmD
Deputy Director for Safety, Division of Cardiology and Nephrology
Office of New Drugs/CDER/FDA

Norman Stockbridge, MD
Director, Division of Cardiology and Nephrology
Office of New Drugs/CDER/FDA

Date: July 8, 2022

Subject: **Cardiovascular safety** of omaveloxolone (NDA 216718)

This memo responds to the consult requesting a review of cardiovascular (CV) events that were reported in the omaveloxolone single Phase 2 trial and recommendations regarding appropriate language for labeling. We received and reviewed the NDA submission package: \\CDSESUB1\evsprod\NDA216718\0003.

DCN Summary and Assessment

The primary safety analysis included a review of the CV events[1] reported in Study 408-C-1402, Part 2 (48-week placebo-controlled), which includes omaveloxolone 150 mg daily (n=51) or placebo (n=52). Individual patient dossiers were also reviewed for those reporting serious CV events or increased BNP during treatment with omaveloxolone.

The results of the analysis include:

- The patient baseline history of CV disease and CV events was not evenly distributed between the treatment groups. More omaveloxolone-treated patients (49%) reported a history of cardiomyopathy than placebo-treated patients (29%).
- The CV events were reported similarly among treatment groups; the estimated annualized rates of CV events per 100-person years were: placebo 29% or 32 per 100 patient-years; omaveloxolone 28% or 33 per 100 patient-years. No trend was observed with respect to the time to onset of any CV event.
- There were no deaths reported in the single Phase 2 trial.

[1] any adverse event reported in the MedDRA System Organ Class (SOC) Cardiac Disorders or Vascular Disorders, and cardiac-related FDA MedDRA Queries (FMQs)

- Although most patient measurements were within normal limits, an increase in BNP was observed for patients treated with omaveloxolone compared to placebo. BNP greater than 100 ng/L and increased from baseline was observed in ten (20%) patients in the omaveloxolone arm and three (6%) in the placebo arm over the course of the trial.

The safety database is too small to characterize omaveloxolone CV safety. A greater baseline history of CV events and cardiomyopathy in the omaveloxolone group than placebo and a high background rate of cardiomyopathy and arrhythmias in FA further complicate interpretation. However, the elevations in BNP levels in the omaveloxolone-treated raise concern for adverse cardiac effects due to the similarities to bardoxolone[2], which shares a similar mechanism and chemical structure, whose phase 3 study in chronic kidney disease patients[3] was discontinued early due to a signal for HF hospitalizations and death.

Background

Reata Pharmaceuticals, Inc. (Applicant) submitted NDA 216718 for omaveloxolone, a new molecular entity (NME) proposed for the treatment of Friedreich's ataxia (FA). Omaveloxolone binds to Keap1, resulting in the activation of nuclear factor-erythroid factor 2-related factor 2 (Nrf2), a transcription factor that modulates the expression of genes involved in regulating mitochondrial function, oxidative stress, and inflammation. The proposed dosage is 150 mg taken orally once daily. The half-life of omaveloxolone is approximately 32-90 hours. Omaveloxolone is not currently approved in any country.

Friedreich's ataxia is a rare, genetic, rapidly progressive, neurodegenerative disorder that affects approximately 5,000 patients in the United States and 22,000 patients globally. Symptoms typically begin between the ages of 5 and 15 years, although they sometimes appear in adulthood. Approximately 15 percent of people with Friedreich ataxia have onset after age 25. FA is strongly associated with a cardiomyopathy, and it is thought that cardiac wall abnormalities are present in most patients, though often these will be asymptomatic (Cook et al, 2017). FA is commonly accompanied by abnormalities of both cardiac structure and function, and cardiac disease is the main cause of death in this condition. Individuals with FA can experience arrhythmias, most commonly of atrial origin, and symptoms due to arrhythmias can include palpitations, dizziness, dyspnea, and chest discomfort. Individuals with FA can also develop heart failure with its associated symptoms, and the combination of heart failure and arrhythmia conveys a poor prognosis. The overall pattern of pathology seems to show a slow regression of left ventricular hypertrophy over time, and a progressive increase in left ventricular dilatation (Regner et al, 2012).

Nonclinical Findings

The Applicant evaluated the toxicity potential of omaveloxolone in studies with daily oral administration for treatment periods of up to 6 months in rats and up to 9 months in monkeys.

[2] Bardoxolone methyl, NDA 215484, received a Complete Response on February 25, 2022. DARRTS Reference ID: 4943446

[3] BEACON was a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study that compared the efficacy and safety of bardoxolone methyl (20 mg; n=1092) to that of placebo (n=1093) in patients with Stage 4 CKD and Type 2 Diabetes receiving standard of care.

Local and systemic toxicity was evaluated in 3-month dermal studies with twice-daily topical administration in rats and minipigs. Cardiovascular safety assessment was conducted in cynomolgus monkeys, which were considered the most relevant for human risk assessment based in part on the similarity of the in vivo metabolite profile. According to the Applicant's submission (Section 4.2.1.3), omaveloxolone produced no effects on cardiovascular function in cynomolgus monkeys at doses up to and including 100 mg/kg. There were no abnormalities in the ECG waveform or morphology that could be directly attributed to administration of omaveloxolone, no changes in CV variables or heart rate, and no significant effects on ECG parameters noted at any omaveloxolone dose.

Nrf2 Activators

There are no approved treatments for FA. There is one product approved in the Nrf2 activator class, dimethyl fumarate (TECFIDERA) indicated for the treatment of relapsing forms of multiple sclerosis. The Applicant also evaluated omaveloxolone in other clinical indications (mitochondrial myopathy and oncology). In addition, the Applicant developed bardoxolone methyl, proposed as a Nrf2 activator and studied in patients with chronic kidney disease (CKD) caused by Alport Syndrome as well as in patients with type 2 diabetes and stage 4 CKD. Bardoxolone has a very similar chemical structure (Figure 6) and mechanism to that of omaveloxolone and carries the CV risks of heart failure and increased BP.[2]

Safety Topic of Interest: CV Safety

Cardiovascular safety was evaluated as a safety topic of interest during the trial because cardiomyopathy is the most common cause of death in patients with FA. In addition, adverse CV events (heart failure and increased blood pressure) were observed in a previous clinical trial for bardoxolone (BEACON [402-C-0903]). During the trial, CV events were not adjudicated by an external committee. To mitigate cardiovascular risks, the Applicant used population selection criteria, excluding patients with:

- B-type natriuretic peptide (BNP) level >200 pg/mL
- History of clinically significant left-sided heart disease and/or clinically significant cardiac disease, with the exception of mild to moderate cardiomyopathy associated with FA, including but not limited to any of the following:
    - Clinically significant congenital or acquired valvular disease
    - Pericardial constriction (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
    - Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screening Visit or within 90 days prior to Screening Visit)
    - Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina)
    - History of hospitalization for heart failure in the last 5 years
    - Cardiac insufficiency, defined as New York Heart Association Class >2
    - History of atrial fibrillation
    - History of unstable arrhythmias
- History of thromboembolic events within the past 5 years
- Taken anticoagulant therapy within 30 days prior to Study Day 1

Proposed Labeling

The proposed labeling includes information regarding increased B-natriuretic peptide (BNP) levels as a Warning in Section 5 (b) (4) (excerpts provided below). There are no CV events listed in Adverse Reactions.

5.3 Elevation of B-natriuretic peptide (BNP)

Treatment with SKYCLARYS (b) (4) increase in (b) (4)

(b) (4) the signs and symptoms of fluid overload, such as sudden weight gain (≥ 3 lb of weight gain in one day, or ≥ 5 lb of weight gain in a week), peripheral edema, and shortness of breath. If signs and symptoms of fluid overload develop, (b) (4)

(b) (4)

Safety Analysis

This review summarizes the CV safety data from 1402-C-408, Part 2. The Applicant submitted a single Phase 2 trial, 1402-C-408, which has two parts. Part 1 was a dose-ranging, randomized, double-blind, placebo-controlled study in 69 patients with FA for 12 weeks. Patients were randomized 3:1 to omaveloxolone at the cohort-specific dose (2.5/5, 10, 20, 40, 80, 160, and 300 mg) or placebo for 12 weeks to allow for selection of the Part 2 dose. Part 2 was a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of omaveloxolone 150 mg in 103 patients with FA for up to 48 weeks. Patients were randomized 1:1 to omaveloxolone (n=51) or placebo (n=52). Safety data proposed in the label is derived from Part 2.

The Applicant also submitted Study 408-C-1402 Open-Label Extension an ongoing, open-label extension study to assess the long-term safety of omaveloxolone in patients with FA who previously completed Study 1402 Part 1 or Study 1402 Part 2. A total of 149 patients are enrolled; patient dossiers for serious CV events reported through the interim database lock date of August 17, 2021, were reviewed for completeness.

Treatment Duration

Treatment duration for omaveloxolone and placebo is provided in Table 1 below. Patients in the omaveloxolone group had a slightly lower time at risk, with approximately 42 patient-years versus 46.6 patient years for placebo. Mean duration of omaveloxolone treatment was approximately 300 days.

Table 1: Study Drug Treatment Duration for Trial 1402-C-408, Safety Population

	Omaveloxolone (N=51)	**PBO (N=52)**
Duration (days)		
Mean (SD)	300.5 (93.5)	327.1 (46.5)
Median	336.0	337.0
Min, Max	17, 355	57, 343
Total time at risk (person-years)	42.0	46.6

PBO=placebo, SD= standard deviation; Source: CSR 1402-C-408 Table 14.1.6.1; Reviewer, JMP, exsum.xpt

Subject Demographics and Baseline Characteristics

Patients were between the ages of 16 and 40 years, consistent with the patient population of FA. There were a greater number of females in the omaveloxolone arm (61%) than placebo (33%). Baseline history of cardiomyopathy was not evenly distributed between the treatment groups, with a higher proportion of patients in the omaveloxolone group (49%) compared with the placebo group (29%). In addition, there was a higher baseline medical history for tachycardia, bundle branch block right, ventricular tachycardia, increased blood CPK, and ECG QT prolonged in the omaveloxolone group (6%, 2%, 2%, 2%, 2%, respectively) versus placebo (0, 0, 0, 0, 0, respectively). The baseline mean left ventricular ejection fraction (LVEF) was similar among treatment groups (Figure 4: omaveloxolone, 64%; placebo, 60%).

Cardiovascular Events

Cardiovascular events are presented in Table 2. The incidence of CV events was similar among treatment groups (placebo 29% or 32 per 100 patient-years; omaveloxolone 28% or 33 per 100 patient-years). Blood CPK increased was the only PT reported in more than 2 patients and greater than placebo. There were a variety of single (n=1) events and overall, no meaningful differences in specific CV events that warranted further subgroup analyses. There were no deaths reported in the trial.

One patient (b) (6) in the omaveloxolone group reported serious adverse events (SAEs) of recurrent palpitations and sinus tachycardia and also reported increased NT-proBNP during the

trial. This patient (with a medical history of tachycardia taking atenolol 25mg daily concomitantly) was treated with antibiotics for respiratory infection concurrently and had a baseline echocardiogram consistent with mild FA cardiomyopathy. The patient was switched to bisoprolol and eventually started on ivabradine to control heart rate; LVEF remained unchanged from baseline at weeks 24 and 48. Another patient (b) (6) reported the SAE, ventricular tachycardia, which was asymptomatic and discovered during a week-4 exercise test; the patient had not taken omaveloxolone for over 2 weeks at the time of discovery due to nonserious increased liver enzymes. The patient remained asymptomatic and had a normal recovery without treatment. Another patient (b) (6) in the treatment arm reported peripheral edema at study day 231; LVEF for this patient remained similar to baseline at week 48.

Table 2. CV Adverse Events[1], Sorted by Risk Difference, for Study 1402-C-408, Part 2, Safety Population

	Omaveloxolone 150 mg (N=51)	**Placebo (N=52)**	**Risk Difference (95% CI)**
Reported CV-related MedDRA PTs[2]	10 (19.6)	13 (25.0)	-5.4 (
Preferred Term			
Atrioventricular block first degree	1 (2.0)	0 (0)	2 (-1.8, 5.8)
Blood creatine phosphokinase increased	3 (5.9)	2 (3.8)	2 (-6.3, 10.3)
Blood pressure increased	1 (2.0)	0 (0)	2 (-1.8, 5.8)
Cardiomyopathy	1 (2.0)	0 (0)	2 (-1.8, 5.8)
Dyspnea	1 (2.0)	0 (0)	2 (-1.8, 5.8)
Edema Peripheral	1 (2.0)	0 (0)	2 (-1.8, 5.8)
N-terminal prohormone brain natriuretic peptide increased	1 (2.0)	0 (0)	2 (-1.8, 5.8)
Sinus tachycardia	1 (2.0)	0 (0)	2 (-1.8, 5.8)
Ventricular tachycardia	1 (2.0)	0 (0)	2 (-1.8, 5.8)
Angina pectoris	1 (2.0)	1 (1.9)	0 (-5.3, 5.4)
Atrial fibrillation	1 (2.0)	1 (1.9)	0 (-5.3, 5.4)
Blood pressure abnormal	0 (0)	1 (1.9)	-1.9 (-5.7, 1.8)
Breath sounds abnormal	0 (0)	1 (1.9)	-1.9 (-5.7, 1.8)
Electrocardiogram T wave inversion	0 (0)	1 (1.9)	-1.9 (-5.7, 1.8)
Heart sounds abnormal	0 (0)	1 (1.9)	-1.9 (-5.7, 1.8)
Left ventricular hypertrophy	0 (0)	1 (1.9)	-1.9 (-5.7, 1.8)
Pulmonary Congestion	0 (0)	1 (1.9)	-1.9 (-5.7, 1.8)
Palpitations	1 (2.0)	2 (3.8)	-1.9 (-8.4, 4.6)
Tachycardia	0 (0)	1 (1.9)	-1.9 (-5.7, 1.8)
Ventricular extrasystoles	0 (0)	2 (3.8)	-3.8 (-9.1, 1.4)
SAE CV-related MedDRA PTs[2]	4 (7.8)	1 (1.9)	5.9 (-2.4, 14.1)
Atrial fibrillation	1 (2.0)	1 (1.9)	0 (5.3, 5.4)
Palpitations	1 (2.0)	0	2 (-1.8, 5.8)
Sinus tachycardia	1 (2.0)	0	2 (-1.8, 5.8)

Table 2. CV Adverse Events[1], Sorted by Risk Difference, for Study 1402-C-408, Part 2, Safety Population

	Omaveloxolone 150 mg (N=51)	Placebo (N=52)	Risk Difference (95% CI)
Ventricular tachycardia	1 (2.0)	0	2 (-1.8, 5.8)
SAE Drug Withdrawn			
Atrial fibrillation	1 (2.0)	1 (1.9)	0 (5.3, 5.4)
Ventricular tachycardia	1 (2.0)	0	2 (-1.8, 5.8)

[1] Includes treatment emergent AE defined as any event that had a start date on or following the first dose of drug up to 30 days following the final dose; patient may have reported >1 PT

[2] MedDRA preferred term from FMQ Acute Coronary Syndrome, FMQ Arrhythmia, FMQ Hypotension, FMQ, Myocardial Infarction, FMQ Myocardial Ischemia, FMQ Palpitations, FMQ Systemic Hypertension, FMQ Heart Failure, FMQ Cardiac Conduction Disturbance, Cardiac Disorders SOC, or Vascular Disorders SOC

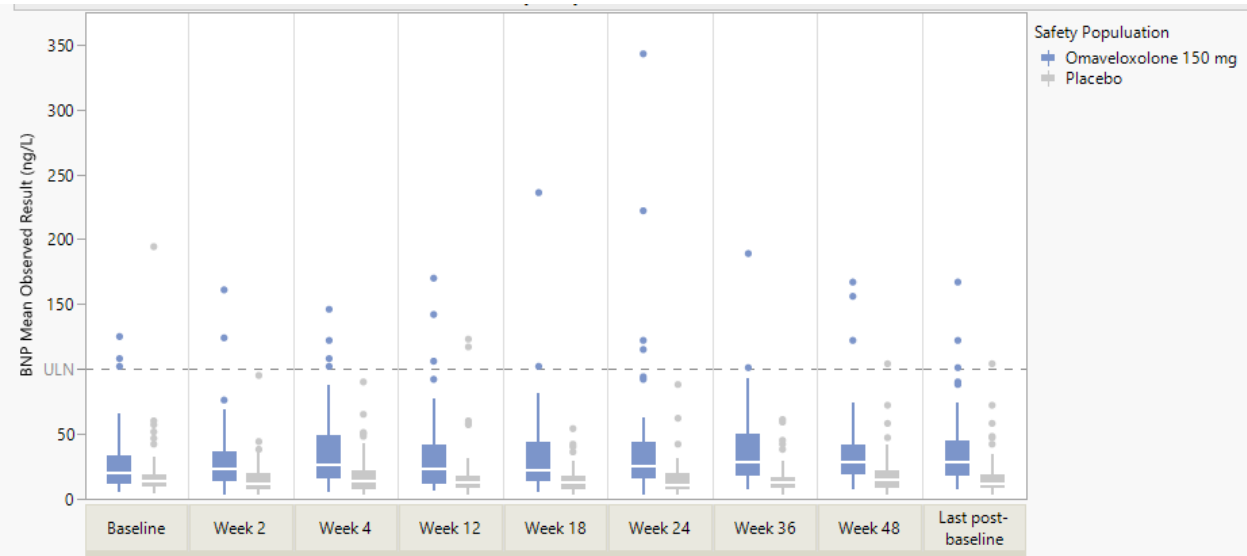
Source: Reviewer's Table; JMP Clinical, OCS Analysis Studio, MAED, adae.xpt, adsl.xpt Abbreviations: CV, cardiovascular; PT, preferred term; SAE, serious adverse event

B-Natriuretic Peptide

Although most patient measurements were within normal limits, an increase in BNP (Figure 1) was observed for patients treated with omaveloxolone compared to placebo. BNP greater than 100 ng/L and increased from baseline was observed in ten (20%) patients in the omaveloxolone arm and three (6%) in the placebo arm over the course of the trial; three of the ten patients in the omaveloxolone arm and all the placebo-treated reported a history of cardiomyopathy. One patient (b) (6) in the omaveloxolone group experienced recurrent BNP levels greater than 200 ng/L; this patient reported a baseline history of cardiomyopathy, and LVEF remained normal and unchanged from baseline. Figure 5 in the appendix provides the BNP change from baseline in patients not reporting a history of cardiomyopathy.

A review of the echocardiogram measurements for the patients with BNP greater than 100 ng/L and increased from baseline revealed decreases in LVEF greater than 5% for one patient (b) (6) in the omaveloxolone-treated, which reported a baseline history of cardiomyopathy, and no patients in the placebo-treated.

Figure 1. Mean BNP Observed Measurement by Visit[1], Trial 1402-C-408, Part 2, Safety Population



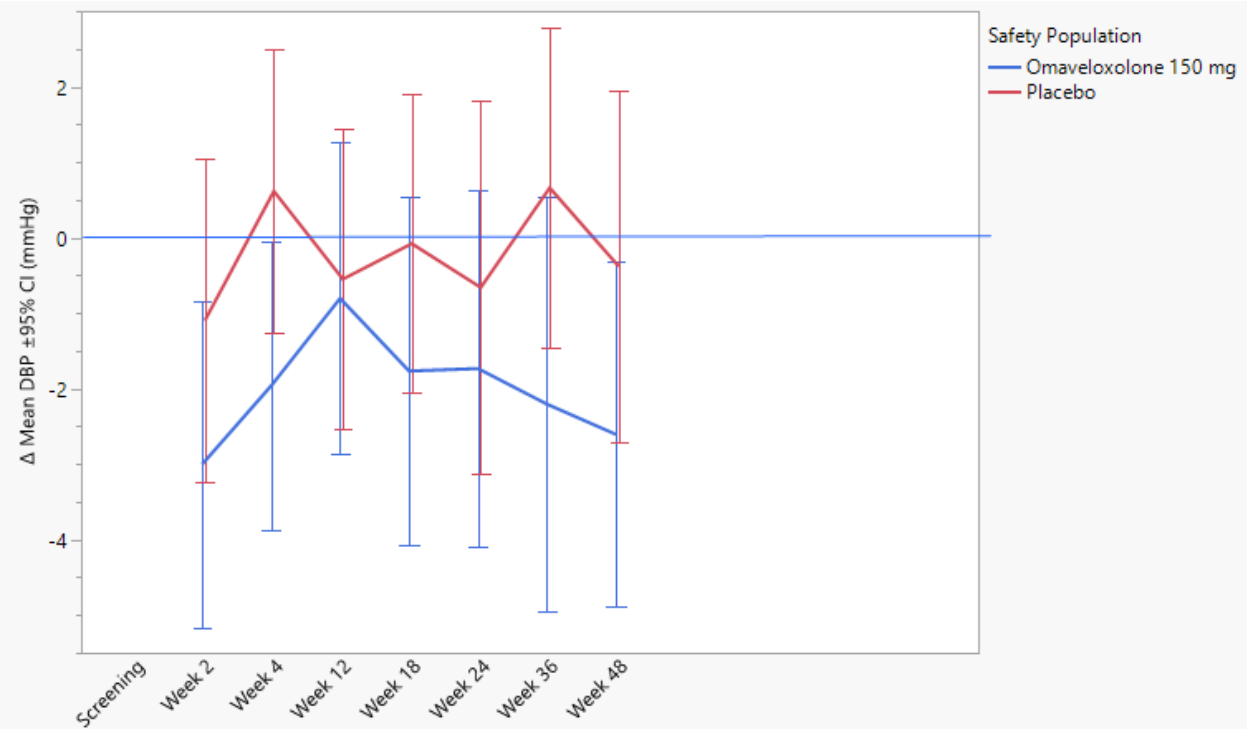
Omav	51	51	48	46	46	42	44	43	51
Placebo	52	52	52	51	51	50	49	50	52
Mean (SD)	29.1 (26)	30.2 (29)	36.3 (32)	34.7 (35)	34.6 (38)	44.4 (62)	37.8 (34)	37.6 (35)	37.4 (32)
Mean (SD)	20.5 (28)	15.8 (15)	20.0 (20)	19.7 (24)	14.5 (11)	15.3 (15)	15.8 (13)	19.2 (19)	18.6 (19)
Max	125.0	161.0	146.0	170.0	236.0	343.0	189.0	167.0	167.0
Max	194.3	95.0	90.0	123.0	54.0	88.0	61.0	104.0	104.0
>ULN and > BL [n (%)]	2 (3.9)	3 (6.3)	2 (4.3)	1 (2.2)	4 (9.5)	1 (2.3)	3 (7.0)	3 (5.9)	
>ULN and > BL [n (%)]	0	0	2 (3.9)	0	0	0	0	1 (1.9)	

Source: Reviewer's Analysis, JMP Clinical, adsl.xpt, adlb.xpt;
[1] Unscheduled visits removed; baseline as last recorded pre-dose measurement
Abbreviations: BL, baseline, BNP, B-natriuretic peptide; Omav, omaveloxolone; SD, standard deviation, ULN, upper limit of normal

Blood Pressure

There were no observed increases from baseline in clinic monitored blood pressure (BP) in the omaveloxolone treatment group. The mean change from baseline and measurements for sitting diastolic and systolic blood pressure are provided in Figures 2-5 below.

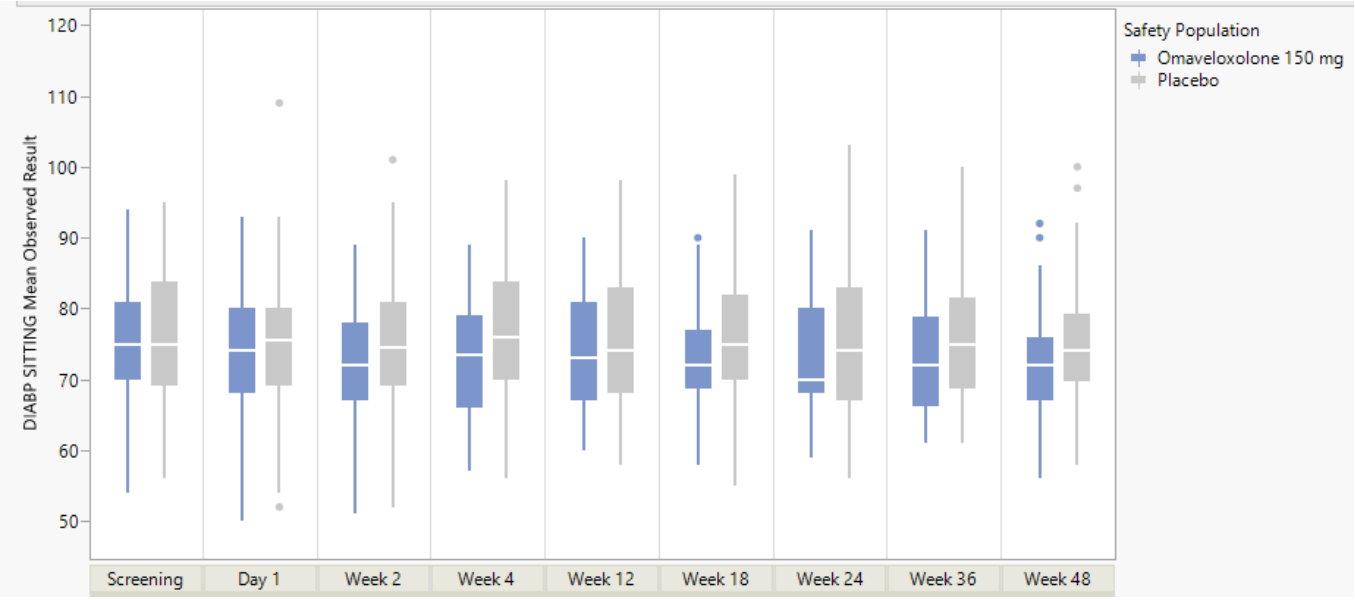
Figure 2. Mean Change from Baseline Diastolic Blood Pressure Measurement by Visit[1], Trial 1402-C-408, Part 2, Safety Population



Omav	51	51	48	46	46	44	44	43
Placebo	52	52	52	51	51	50	50	50

Source: Reviewer's Analysis, JMP Clinical, advs.xpt
[1] Unscheduled visits removed; baseline as last recorded pre-dose measurement
Abbreviations: DBP, diastolic blood pressure; CI, confidence interval; Omav, omaveloxolone

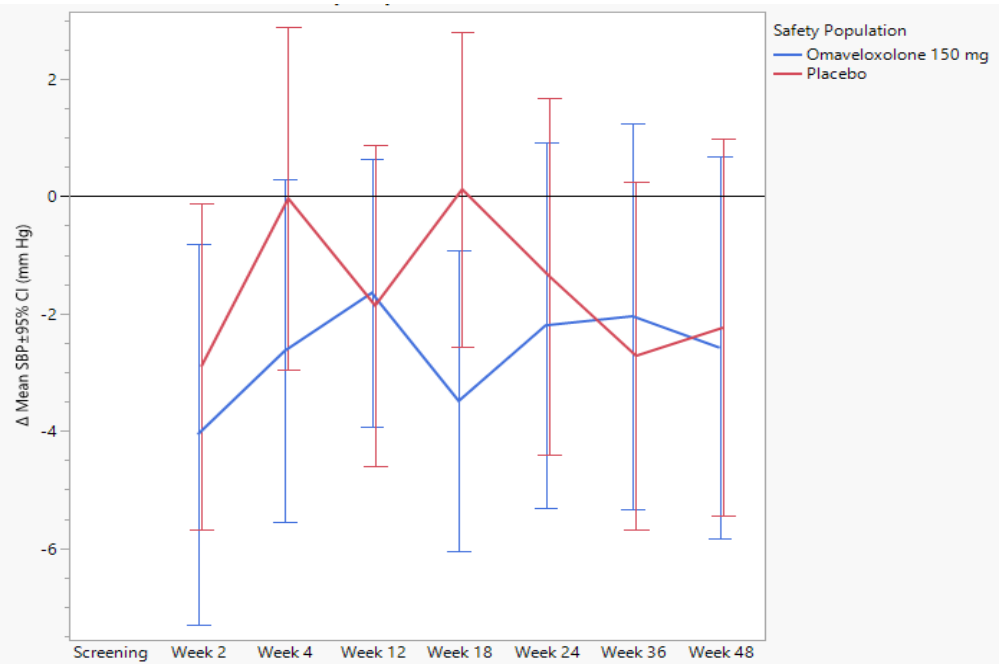
Figure 3. Mean Sitting Diastolic Blood Pressure Measurement by Visit[1], Trial 1402-C-408, Part 2, Safety Population



Omav	51	51	51	48	46	46	44	44	43
Placebo	52	52	52	52	51	51	50	50	50
Mean (SD)	75.7 (8)	73.4 (9)	71.8 (9)	72.9 (8)	73.8 (8)	73.3 (7)	73 (8)	72.5 (8)	72.3 (8)
Mean (SD)	76 (9)	75.2 (10)	74.7 (10)	76.4 (9)	75.2 (9)	75.6 (9)	75.1 (10)	76.4 (9)	75.4 (9)
Max	94	93	89	89	90	90	91	91	92
Max	95	109	101	98	98	99	103	100	100

Source: Reviewer's Analysis, JMP Clinical, advs.xpt
[1] Unscheduled visits removed; baseline as last recorded pre-dose measurement
Abbreviations: DIABP, diastolic blood pressure; Omav, omaveloxolone; SD, standard deviation

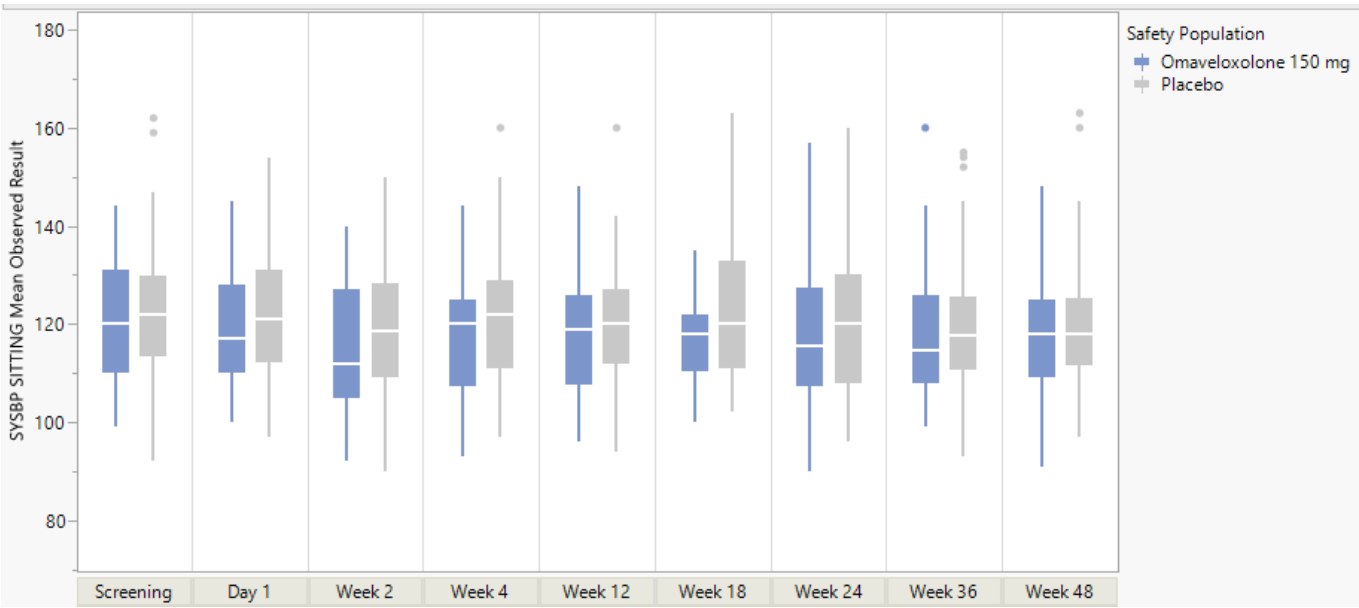
Figure 4. Mean Change from Baseline Systolic Blood Pressure Measurement by Visit[1], Trial 1402-C-408, Part 2, Safety Population



Omav	51	51	48	46	46	44	44	43
Placebo	52	52	52	51	51	50	50	50

Source: Reviewer's Analysis, JMP Clinical, advs.xpt
[1] Unscheduled visits removed; baseline as last recorded pre-dose measurement
Abbreviations: Omav, omaveloxolone; SBP, systolic blood pressure; CI, confidence interval

Figure 5. Mean Sitting Systolic Blood Pressure Measurement by Visit[1], Trial 1402-C-408, Part 2, Safety Population



Omav	51	51	51	48	46	46	44	44	43
Placebo	52	52	52	52	51	51	50	50	50
Mean (SD)	120.3 (12)	118.5 (12)	115.5 (13)	117.3 (12)	118.5 (12)	116.4 (9)	117.6 (14)	117.7 (13)	117.4 (13)
Mean (SD)	122.3 (15)	121.9 (12)	119.4 (14)	122.3 (14)	120.4 (13)	122.4 (14)	121.1 (15)	119.8 (14)	120.3 (13)
Max	144	145	140	144	148	135	157	160	148
Max	162	154	150	160	160	163	160	155	163

Source: Reviewer's Analysis, JMP Clinical, advs.xpt
[1] Unscheduled visits removed; baseline as last recorded pre-dose measurement
Abbreviations: Omav, omaveloxolone; SYSBP, systolic blood pressure; SD, standard deviation

The lack of observed BP effects of omaveloxolone is not reassuring, given this trial is not powered to detect small, but potentially clinically meaningful increases in BP. The Applicant used clinic measurements which cannot capture BP changes that occur naturally throughout the day and clinic monitoring is associated with measurement error and increased variability. The Agency recommends ambulatory blood pressure monitoring (ABPM) for drugs intended for chronic use, if a large BP effect is not detected by clinical measurements in early, small trials. ABPM provides more accurate measurements of BP throughout the day and can detect small changes in BP (nocturnal), which we know impacts a person's CV risk over time.

QT Interval

Analysis of QT data are beyond the scope of this memo; a separate QT-IRT consult was requested.

Discussion

Many factors limit the conclusions that can be drawn about the cardiovascular safety of omaveloxolone, including the size of the study population, the high background rate of CV mortality in patients with FA, the failure of randomization regarding baseline history of cardiomyopathy, and the use of clinic monitoring for BP. Overall, given the FA patient

population and small trial, we cannot make any conclusions regarding CV safety and there are no larger double-blind, placebo-controlled trials for other indications that we can refer to for additional safety data. However, the observations in the omaveloxolone-treated are similar to those observed with a drug in the same pharmacologic class, bardoxolone, and the elevations in BNP levels raise concern for adverse cardiac effects. We believe these are plausible potential risks for omaveloxolone.

Conclusion

The CV safety cannot be determined because there was a greater baseline history of CV events and cardiomyopathy in the omaveloxolone group than placebo, a high background rate of cardiomyopathy and arrhythmias in FA, and small trial population. In addition, ABPM was not used for BP monitoring. However, the elevations in BNP levels in the omaveloxolone-treated raise concern for adverse cardiac effects due to the similarities to bardoxolone, which is structurally and pharmacologically similar and whose study in CKD patients was discontinued early due to a signal for HF hospitalizations or HF death.

References

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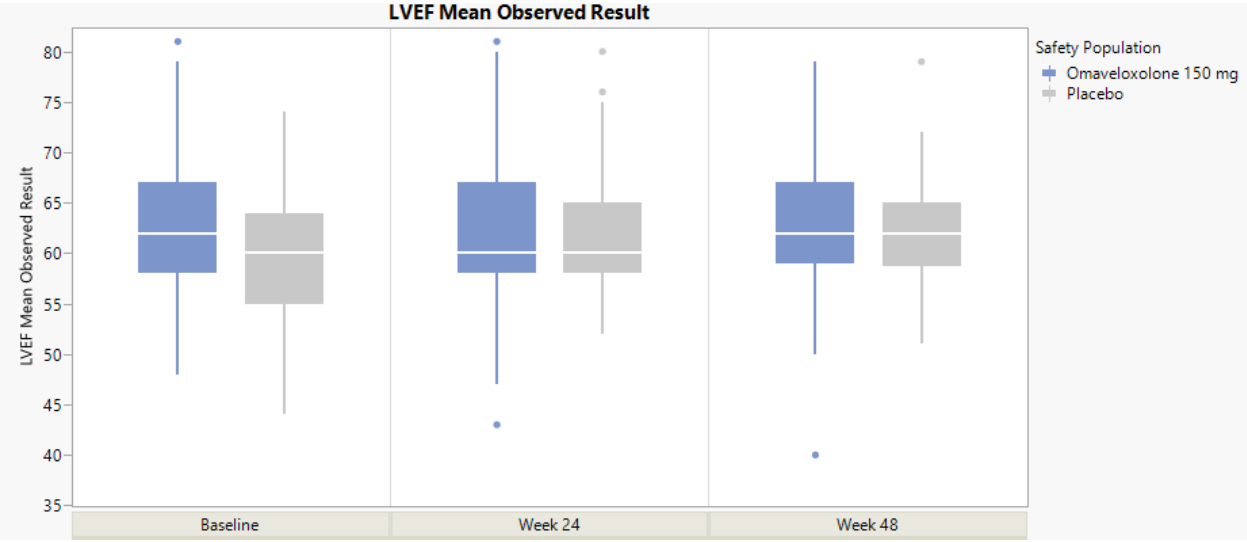
Regner, S. R., Lagedrost, S. J., Plappert, T., Paulsen, E. K., Friedman, L. S., Snyder, M. L., Perlman, S. L., Mathews, K. D., Wilmot, G. R., Schadt, K. A., Sutton, M. S., & Lynch, D. R. (2012). Analysis of echocardiograms in a large heterogeneous cohort of patients with friedreich ataxia. *The American journal of cardiology, 109(3)*, 401–405. https://doi.org/10.1016/j.amjcard.2011.09.025

Appendices

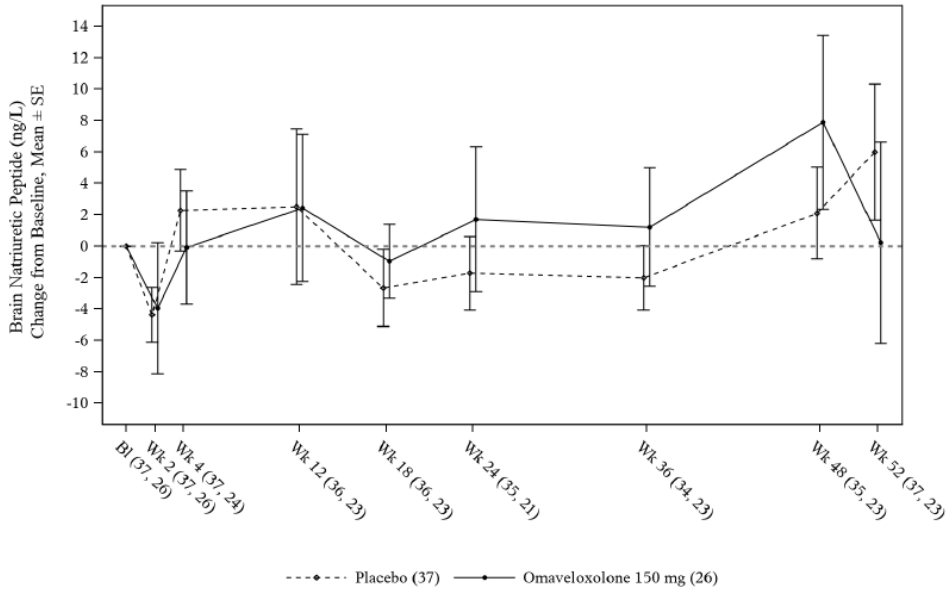
Figure 4: Mean LVEF Measurements by Visit[1], Trial 1402-C-408, Part 2, Safety Population



Omav	51	44	43
Placebo	52	49	50
Mean (SD)	63.5 (8)	62.4 (9)	63.2 (7)
Mean (SD)	59.8 (6)	61.6 (6)	62.0 (5)
Min	48	43	40
Min	44	52	51

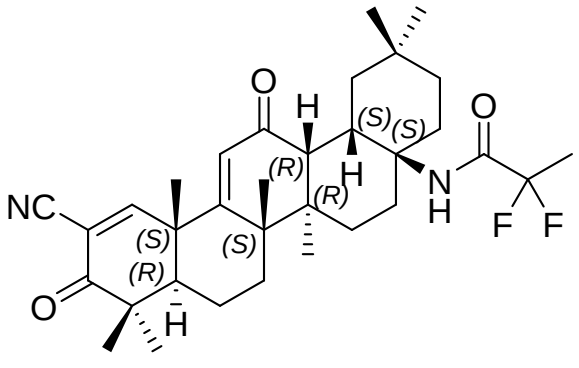
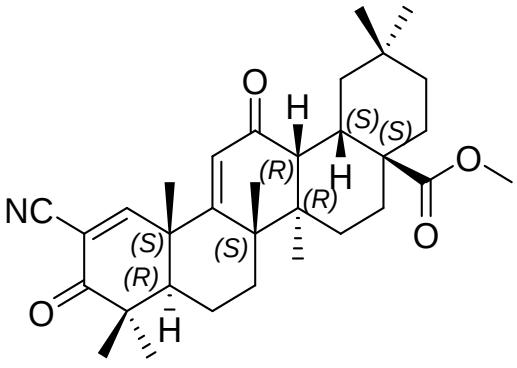
Source: Reviewer's Analysis, JMP, adlb.xpt
[1] Unscheduled visits removed; baseline as last recorded pre-dose measurement
Abbreviations: LVEF, left ventricular ejection fraction; Omav, omaveloxolone; SD, standard deviation

Figure 5: BNP Change from Baseline through Week 52 by Visit in FA Patients Without History of Cardiomyopathy



Source: CSR 408-C-1408-PT2 Figure 14.3.4.9

Figure 6. Omaveloxolone and Bardoxolone methyl Chemical Structures

Omaveloxolone	Bardoxolone methyl
	
Mechanism of Action	Mechanism of Action
Omaveloxolone selectively and reversibly binds to Keap1, resulting in the activation of Nrf2, a	Bardoxolone methyl binds to Keap1, resulting in the activation of

transcription factor that modulates the expression of genes involved in regulating mitochondrial function, oxidative stress, and inflammation. Omaveloxolone activity is dependent on the Keap1-Nrf2 pathway. By activating this pathway, omaveloxolone modulates the transcription of genes that protect the cell by three complementary and overlapping mechanisms: • Inhibits proinflammatory signaling pathways, including the nuclear factor-kappa B (NF-κB) pathway, and reduces the production of pro-inflammatory mediators. • Increases the expression of antioxidative enzymes, elevates the levels of endogenous antioxidants, and reduces oxidative stress. • Modulates pathways involved in cellular metabolism and mitochondrial function.	Nrf2, a transcription factor that modulates the expression of genes involved in regulating inflammation, oxidative stress, and cellular energy metabolism. Bardoxolone methyl activity is dependent on the Keap1-Nrf2 pathway. By activating this pathway, bardoxolone methyl modulates the transcription of genes that protect the cell by three complementary and overlapping mechanisms: • Inhibits proinflammatory signaling pathways, including the nuclear factor-kappa B (NF-κB) pathway, and reduces the production of pro-inflammatory mediators. • Increases the expression of antioxidative enzymes, elevates the levels of endogenous antioxidants, and reduces oxidative stress. • Modulates pathways involved in cellular metabolism and mitochondrial function.

Source: Reviewer's Table; (b) (4)

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