Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Omaveloxolone

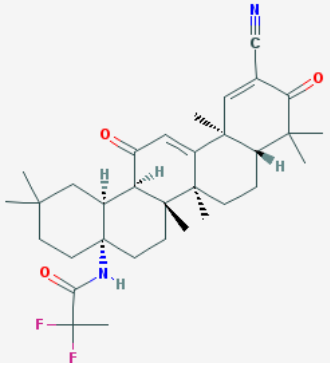
Evidence Summary

It may help protect mitochondria against oxidative stress damage in pathological conditions, and reduce inflammation with treatment starting as early as possible. It has been well tolerated in clinical trials.

Neuroprotective Benefit: It may help protect against neuroinflammation, mitochondrial damage in neurons and preserve motor function. Potential effects on cognition have not been established and is likely most effective very early or prior to symptom onset.

Aging and related health concerns: It increases resistance of mitochondria to oxidative stress damage in mitochondrial diseases, but it is unknown if it can also protect mitochondria in the context of aging.

Safety: It was well tolerated based on clinical trials. Common effects included nausea, fatigue, and transient aminotransferase elevations, which resolve over time as tolerability develops. The long-term safety profile needs to be determined.

Availability: Rx	**Dose**: 150 mg daily oral capsules (Friederich's ataxia)	**Chemical formula:** $C_{33}H_{44}F_2N_2O_3$ **MW**: 554.723 g/mol
Half-life: Mean 57 hours	**BBB**: penetrant	 Source: Pubchem
Clinical trials: One Phase 2 for mitochondrial myopathy (n=53), Phase 2/3 trial for Friederich's ataxia (n=69, n=103) show possible benefit. Phase 2 trials for cancer (n=41), radioprotection (n=187), and protection against cornea damage (n=304).	**Observational studies**: None	

What is it?

Omaveloxolone (RTA-408) is a second generation orally bioavailable synthetic oleanane triterpenoid developed by Reata Pharmaceuticals as an activator of the Nrf2 antioxidant pathway. It has been tested in clinical trials for mitochondrial diseases, cancer, and to protect against radiotherapy-induced skin damage and ophthalmic surgery induced corneal damage. In February 2023, omaveloxolone was approved for the treatment of Frederich's ataxia in patients ≥ 16 years old, and is marketed as SKYCLARYS®. In July 2023, Reata Pharmaceuticals was acquired by Biogen (Press release).

Neuroprotective Benefit: It may help protect against neuroinflammation, mitochondrial damage in neurons and preserve motor function. Potential effects on cognition have not been established and is likely most effective very early or prior to symptom onset.

Types of evidence:

- 1 RCT assessing neurological function in Friederich's ataxia
- 5 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

There have been no studies in humans directly examining the effects of omaveloxolone on cognition. The mechanism of action involves preservation of mitochondria in the context of cellular stressors. In an RCT for patients with Friedreich's ataxia, treatment with omaveloxolone was associated with improved neurological function as measured by the modified Friedreich Ataxia Rating Scale (mFARS), which is primarily an assessment of motor function and ataxia [1]. Although this does not provide evidence for potential cognitive benefit, it does provide evidence for potential neuroprotective benefit.

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Amyotrophic lateral sclerosis: POTENTIAL BENEFIT IN PRODROMAL STAGE (preclinical)
Omaveloxolone protected against ferroptosis-mediated cell death in cells containing the hSOD1G93A ALS-associated mutation [2]. In mice containing the hSOD1G93A mutation, treatment with omaveloxolone (1 mg/kg i.p. twice weekly for six weeks) starting at 2.5 months of age protected against body weight loss, neuronal loss, and pathological changes to mitochondrial morphology [2]. The treated ALS mice also had better motor performance on the rotarod test relative to their untreated counterparts. It is unclear whether omaveloxolone would offer benefit following the onset of pathology and motor deficits.

Epilepsy: POTENTIAL BENEFIT (preclinical)
In a kainic acid mouse model of epilepsy, omaveloxolone treatment following seizure induction restored glutathione and ATP levels and reduced neuronal loss in the hippocampus [3]. The mechanism of protection from excitotoxicity may involve protecting neuronal mitochondria. Pre-treatment of cortical neurons with omaveloxolone prevented mitochondrial depolarization and neuronal death during epileptiform activity. This suggests that omaveloxolone may protect neuronal mitochondria from excitotoxic stress, though it remains to be determined whether this protection extends to other types of neuronal stressors.

Anesthesia-related cognitive impairment: POTENTIAL BENEFIT (preclinical)
Omaveloxolone protected against propofol-induced cognitive impairment in neonatal mice based on performance on the Morris water maze [4]. It mitigated the propofol-mediated induction of NF-kB, pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β), and caspase-3-induced neuronal cell death via the activation of Nrf2. This suggests that omaveloxolone may help protect against acute inflammation and

oxidative-stress-mediated cognitive impairment, though it is unclear whether it would offer similar benefit to older animals with less robust endogenous antioxidant-induction capacity and/or in the context of chronic disease.

Neuroinflammation: Along with the preservation/restoration of mitochondrial function, the mitigation of inflammation is expected to be one of the neuroprotective primary mechanisms of omaveloxolone. Activation of Nrf2 can inhibit the pro-inflammatory NF-kB signaling pathway. In cultured rat astrocytes, treatment with omaveloxolone attenuated reactive oxygen species (ROS) production, NF-kB activation, and matrix metalloprotease-9 (MMP-9) induction in response to IL-1β [5]. It has not been established which cell types are the primary targets of omaveloxolone *in vivo*.

Intracerebral hemorrhage: POTENTIAL BENEFIT (preclinical)
In the context of oxygen-hemoglobin stress, omaveloxolone promoted the induction of Nrf2 in cultured BV2 microglial cells [6]. The induction of Nrf2 was accompanied by the expression of antioxidant proteins, a reduction in the generation of ROS, and preservation of the mitochondrial potential. Omaveloxolone attenuated the transition of the microglia toward a pro-inflammatory M1-like state, and instead enhanced the polarization into a neuroprotective M2-like state. Similarly, treatment with omaveloxolone (10 mg/kg i.p.) 30 minutes after induction of intracerebral hemorrhage in a mouse model and continued for the next two days, resulted in a lower hematoma volume, reduced residual hemoglobin content, reduced pro-inflammatory cytokines (TNF-α, IL-1β), and a higher proportion of M2-like microglia in the perihematomal region.

***APOE4 interactions*:** Unknown

Aging and related health concerns: It increases resistance of mitochondria to oxidative stress damage in mitochondrial diseases, but it is unknown if it can also protect mitochondria in the context of aging.

Types of evidence:

- 3 clinical trials (Phase 2 placebo controlled RCTs, 1 Phase 1b/2 open-label trial)
- Numerous laboratory studies

Mitochondria-associated diseases: The results of 2 Phase 2 RCTs, while preliminary and underpowered, provide support for a possible beneficial effect of omaveloxolone on mitochondrial function in humans.

However, it is not yet known whether omaveloxolone can protect against age-related mitochondrial dysfunction.

Mitochondrial myopathy: POTENTIAL MINOR BENEFIT MAY NOT BE CLINICALLY MEANINGFUL
In a Phase 2 RCT (MOTOR NCT02255422) (n=53) patients with mitochondrial myopathy (age 18-75) were treated with omaveloxolone (5 to 160 mg) for 12 weeks [7]. There were no significant effects on the primary outcome of the change in peak cycling exercise workload or the secondary outcome of the 6-minute walk test (6MWT) distance at any of the doses, and secondary outcomes of peak work and the distance walked in 6 min walk test, respectively. However, in submaximal exercise testing at week 12, patients treated at the 160 mg dose demonstrated a significant lowering of heart rate at week 12 (by 12.0 ± 4.6 bpm vs placebo, p = 0.01, and by 8.7 ± 3.5 bpm vs baseline, p = 0.02), and blood lactate (by 1.4 ± 0.7 mM vs placebo, p = 0.04, and by 1.6 ± 0.5 mM vs baseline, p = 0.003). These measures are indicative of improved mitochondrial function. Omaveloxolone led to Nrf2 induction in these patients based on the pharmacodynamic measure of increased ferritin levels. Based on the results of this study Reata Pharmaceutical does not appear to be continuing clinical development of omaveloxolone for this indication, at this time.
In cultured primary fibroblasts from patients with mitochondrial diseases, including mitochondrial complex I deficiency, mitochondrial cytochrome oxidase deficiency, Parkin-related Parkinson's disease, and DJ-1 related Parkinson's disease, treatment with omaveloxolone (50 nM) improved mitochondrial bioenergetics, including mitochondrial mass, mitochondrial DNA content, and energy status [8]. With the exception of the DJ-1 mutant cells, omaveloxolone did not significantly impact ATP production or ROS levels. Omaveloxolone also positively impacted oxygen consumption rates in the Parkinson's disease cells. Additionally, omaveloxolone increased basal oxygen consumption, and maximal capacity in healthy control cells, in conjunction with a decrease in ROS. This study suggests that omaveloxolone can have a positive impact on mitochondrial bioenergetics in both healthy cells and those with mitochondrial deficits, but that its potential for therapeutic benefit likely varies depending on the nature of the mitochondrial deficit.

Friedreich's ataxia: BENEFIT
Friederichs's ataxia is a progressive neurodegenerative disease of the spinal cord that affects motor function. It is caused by a mutation in the mitochondrial protein frataxin, which leads to mitochondrial complex I inhibition. Mitochondria in these patients are particularly vulnerable to oxidative stress. *In vitro* studies using patient derived cells suggest that omaveloxolone can increase the resistance of mitochondria to oxidative stress by increasing glutathione levels [9].

In the Phase 2 range dosing part (Part 1) of a Phase2/3 RCT (MOXIe NCT02255435) with Friedreich's ataxia patients (n=63), the primary outcome measure of peak work load in maximal exercise testing (0.9 ± 2.9 W, placebo corrected) was not significant relative to placebo [10]. Omaveloxolone-treated patients showed improvement by 3.8 points (significant) relative to baseline (P = 0.0001) and by 2.3 points (trend) relative to placebo (P = 0.06) on the mFARS, which is a measure of neurological function, at the 160 mg dose. Patients without foot deformities showed the greatest benefit, with an improvement on the mFARS by 6.0 points from baseline (P < 0.0001) and by 4.4 points versus placebo (P = 0.01) at this dose. However, the n's are very small and this finding may stem from the presence of the deformity confounding the testing.

In Part 2 of this study (n=103 enrolled; n=82 analyzed), Friedreich's ataxia patients with mFARS scores between 20 and 80, (maximum score of 93), where higher scores indicate more disability, were randomized 1:1 to 150 mg/day omaveloxolone or placebo for 48 weeks [1]. The primary outcome was change in mFARs, which has four subsections, bulbar, upper limb coordination, lower limb coordination, and upright stability. Omaveloxolone treatment led to a significant improvement in mFARS scores relative to baseline (−1.55 ± 0.69 points, 95% confidence interval [CI] −2.93 to −0.18, df = 72.6) and placebo (–2.40 ± 0.96 points, 95% CI −4.31 to −0.5; p = 0.014). There were improvements in each of the four subsections, with the greatest effect seen in upright stability. Pediatric patients (<18 years old) showed the greatest benefit. There was nominal statistical significance on the secondary endpoint of Friedreich's ataxia-activities of daily living (FA-ADL) relative to placebo (−0.17 ± 0.45 vs 1.14 ± 0.42, p = 0.042), and trends toward improvement with omaveloxolone on the other secondary endpoints of patient global impression of change (PGIC) and the clinical global impression of change (CGIC), which are assessments of pain. Similar to Part 1 of this study, patients without the presence of the foot deformity showed greater improvement on the mFARS, which is thought to be related to a limitation of the mFARS measure rather than reflective of a meaningful biological difference in efficacy between these two subpopulations. In both parts of this study, treatment with omaveloxolone showed pharmacodynamic evidence of activity, based on an increase in ferritin levels.

The difference in mFARS between those originally assigned to omaveloxolone (n=29) and those originally assigned to placebo (n=29) was maintained during the 72-week open-label extension period (−2.91 ± 1.44 points), and omaveloxolone patients continued to show a lack of worsening throughout the extension period, suggestive of continued benefit [11]. These results are particularly notable because the omaveloxolone group had more severe disease and a higher percentage of patients with cardiomyopathy at baseline, relative to the placebo group. Similarly, when patients in the MOXIe extension trial (n=136) were compared to matched participants (n=136) in the untreated longitudinal Friedreich ataxia Clinical Outcome Measures Study (FACOMS), trial participants showed a lower degree

of worsening (difference = −3.6) on the mFARS [12]. In those initially receiving omaveloxolone, mFARS progression was slowed by 61% from extension study baseline relative to FACOMS participants, while it was slowed by 56% in those who started with placebo and then switched to omaveloxolone during the open-label extension. These studies suggest that earlier treatment appears to be more effective and that the benefits are maintained with continued treatment. In light of these results, omaveloxolone was approved by the FDA for Friedreich's ataxia in patients sixteen and older in February 2023 (FDA Press release).

Radiation damage: POTENTIAL BENEFIT (preclinical)
Triterpenoids have been shown to provide protection of healthy cells from radiation damage in rodent models. In mice receiving a lethal dose (0% survival after 30 days) of radiation (8Gy IR), omaveloxolone pre-treatment prevented lethality (100% survival after 30 days) by preserving the integrity of the intestinal lining [13]. Furthermore, when used in combination with radiotherapy in a prostate cancer tumor xenograft model, omaveloxolone enhanced the inhibition of tumor growth compared to radiation alone (p=0.001). Omaveloxolone also protected against chronic radiation (40 Gy) toxicity in rats [14; 15]. It prevented tissue necrosis, preserved the vascular integrity, and induced adipogenesis/angiogenesis gene transcriptional programs in the skin. Omaveloxolone was also shown to promote wound healing in rodent models of chronic venous insufficiency and diabetes [16; 17].
In light of these positive preclinical results, omaveloxolone was tested as an adjunct for cancer patients receiving radiotherapy. A lotion containing 3% omaveloxolone has shown a good safety profile in healthy volunteers [18], but the results of the Phase 2 RCT (PRIMROSE NCT02142959) testing its ability to protect against radiation induced dermatitis in breast cancer patients has not been made available, despite concluding in 2015. If demonstrated to be effective in humans, this type of lotion could potentially also be useful to protect against damage from everyday sources of environmental radiation.

Cancer: MINOR OR NO SIGNFICANT BENEFIT IN CLINICAL STUDIES
Compounds with a primary mechanism of action of Nrf2 activation, such as omaveloxolone, are generally most effective when used for prevention or early-stage intervention, but thus far it has only been tested in late-stage cancer. Omaveloxolone was tested in a Phase 1 (DISCOVER NCT02029729) study in patients with stage 4 solid tumor cancer (primarily) NSCLC or melanoma but did not prevent disease progression in this study [19]. However, the highest dose (15mg) was much lower than the therapeutic dose (160 mg) in the mitochondria-disease trials. Omaveloxolone (up to 100 mg) has also been tested in a Phase 1b/2 non-randomized open-label trial (REVEAL NCT02259231) as an adjunct (to ipilimumab or nivolumab) in stage 3/4 metastatic melanoma patients. The primary outcome was overall

response rate, with best overall response rate defined as "the proportion of patients with complete or partial tumor size reduction according to RECIST v1.1 criteria." Best overall responses occurred in 6/6 at the dose of 5 mg & ipilimumab, 0/3 with 10 mg & ipilimumab, 5/6 with 5 mg & nivolumab, 2/4 with 10 mg & nivolumab, 3/5 with 20 mg & nivolumab, 3/5 with 100 mg & nivolumab, and 4/5 with 150 mg & nivolumab. Reata Pharmaceuticals does not appear to be continuing the development of omaveloxolone for cancer.

Omaveloxolone and bardoxolone methyl were found to inhibit MYB gene activity and facilitate apoptosis in numerous T-cell acute lymphoblastic leukemia cell lines [20]. Notably, the impact to the cancer cell lines was achieved at low nanomolar concentrations which did not adversely affect healthy bone marrow cells. Omaveloxolone (20 mg/kg) prevented the growth of squamous cell carcinoma tumor cells in a mouse model, while topical omaveloxolone (3% w/v) reduced the severity of skin lesions in a mouse model of epidermolysis bullosa [21].

Neuropathy: POTENTIAL BENFIT (preclinical)

In a mouse model of neuropathic pain, chronic constriction injury (CCI) of the sciatic nerve, intrathecal omaveloxolone treatment reversed mechanical allodynia and thermal hyperalgesia in a dose-dependent manner [22]. The analgesic effect was dependent on the Nrf2-mediated induction of PGC-1α, the regulator of mitochondrial biogenesis. However, omaveloxolone failed to show neuroprotective activity in a rat model of ischemic optic neuropathy [23]. A related synthetic triterpenoid activator of Nrf2, bardoxolone (RTA-402), did protect against retinal ganglion cell loss in this model. The reason for the differential efficacy of bardoxolone and omaveloxolone in this model is unclear.

Osteoporosis: POTENTIAL BENEFIT (preclinical)

Bone reabsorbing osteoclast differentiation is initiated by receptor activator of nuclear factor-κB ligand (RANKL), and this process leads to the production of ROS [24]. Omaveloxolone was found to inhibit RANKL-mediated osteoclastogenesis. The inhibition of RANKL was related to the ability of Nrf2 to suppress STING. Treatment with omaveloxolone was found to inhibit osteoclast differentiation and bone resorption in cell culture and to attenuate bone loss in the mouse model of ovariectomy-induced bone loss by reducing the production of osteoclasts.

Osteoarthritis: POTENTIAL BENEFIT (preclinical)

Nrf2 levels were found to be significantly lower in primary chondrocytes from older adults and those with osteoarthritis relative to young adults [25]. This is consistent with the age-related decline in Nrf2 induction. Treating these osteoarthritis chondrocytes with omaveloxolone *ex vivo* promoted the

activation of Nrf2 as well as a reduction in the activation of NF-kB and an improvement in the response to IGF-1 [25]. In a destabilized medial meniscus surgery-induced model of osteoarthritis, rats treated with omaveloxolone (200 or 500 µg/kg i.p every 3 days) resulted in higher utilization of the affected limb, suggestive of reduced pain [26]. Additionally, omaveloxolone led to increased production of collagen type II and aggrecan, as well as better bone microarchitecture, relative to untreated rats with osteoarthritis. In cell culture, omaveloxolone treatment reduced the induction of oxidative stress markers (ROS generation, SOD and MDA), and pro-inflammatory NF-kB signaling.

Nonalcoholic steatohepatitis: POTENTIAL BENFIT (preclinical)
In the STAM model of NASH, omaveloxolone treatment (10 mg/kg orally) reduced NAFLD activity score, hepatic fat deposition, hepatocellular ballooning, inflammatory cell infiltration, and collagen deposition [27]. Treatment also improved blood glucose control based on reductions in non-fasting blood glucose and glycated hemoglobin A1C concentrations. While there were reductions in liver and serum triglycerides, there were elevations in serum total, HDL, and LDL cholesterol. The effect on cholesterol is thought to be related to improved fat mobilization, fatty acid oxidation, and mitochondrial function. Nrf2 regulates the expression of cholesterol efflux transporters and regulates enzymes important for fatty acid beta oxidation. Serum levels of leptin were decreased, while levels of adiponectin were increased. The anti-inflammatory and anti-fibrotic effects were likely mediated by the activation of Nrf2 in the liver, as indicated by the induction of Nrf2 target genes, including NQO1 and ferritin heavy chain.

Asthma: POTENTIAL BENFEIT (preclinical)
In OVA-sensitized mice exposed to ozone, pretreatment with omaveloxolone (17.5 mg/kg i.p.) attenuated ROS production and specific airway resistance [28]. Pretreatment prevented airway hyperresponsiveness, reduced the infiltration of neutrophils and eosinophils into the lungs, and reduced levels of pro-inflammatory cytokines and chemokines (IL-17A, IL-4, IFN-γ, MCP-1, and KC). Pretreatment with omaveloxolone also prevented the loss of barrier integrity and inflammatory cytokine production (IL-6 and IL-1β) in mouse lung slices exposed to organic dust extract and hydrogen sulfide [29].

Antiviral: POTENTIAL BENEFIT (preclinical/ *in vitro*)
Omaveloxolone was found to have antiviral properties against new world alpha viruses, including Venezuelan Equine Encephalitis Virus (VEEV) and Eastern Equine Encephalitis Virus (EEEV), which are mosquito-transmitted viruses which lead to CNS infections in humans and horses [30]. Omaveloxolone along with the related synthetic oleanane triterpenoid Nrf2 activator bardoxolone methyl, showed broad-spectrum antiviral activity, at concentrations ranging from 0.5 to 1 µM, against multiple strains of

VEEV and EEEV in multiple cell lines, including microglial and astrocytic cells. Omaveloxolone and bardoxolone methyl also showed protection against VEEV viral load and neuroinflammation in an organ on a chip model of the neurovascular unit [31]. It has not yet been established whether omaveloxolone shows antiviral activity *in vivo* or protects against additional viruses or pathogens.

Safety: It was well tolerated based on clinical trials. Common effects included nausea, fatigue, and transient aminotransferase elevations, which resolve over time as tolerability develops. The long-term safety profile needs to be determined.

Types of evidence:

- 4 clinical trials (2 Phase 1, 2 Phase 2 RCT)
- Numerous laboratory studies

The majority of adverse events reported in clinical trials have been mild or moderate. The most common involve gastrointestinal events during the first several weeks, which resolve with continued treatment as tolerability develops. Due to the mechanism of Nrf2 activation, cases of aminotransferase liver enzyme elevations have occurred, however, these appear to be related to Nrf2-mediated increases in aminotransferase gene transcription, as they occurred in the absence of other markers of liver injury, such as increases in bilirubin. Aminotransferase elevations have also been seen in clinical trials for the related synthetic oleanane triterpenoid Nrf2 activator, bardoxolone.

In a dose escalation study testing up to 15 mg/day in oral capsules in cancer patients, the most common adverse events were elevated phosphatase (2/11) and anemia (2/11) [19]. Heart function was not negatively affected based on serial ECG and plasma B-type natriuretic peptide (BNP) levels.
In patients with mitochondrial myopathy, 160 mg omaveloxolone was well-tolerated, and most adverse events were mild to moderate [7]. The most common adverse events include headache, nausea, increased alanine (ALT) and aspartate (AST) aminotransferase, fatigue, diarrhea, and abdominal pain. Adverse events generally occurred during the first 12 weeks, after which tolerability developed. Serious adverse events occurred in three patients with omaveloxolone, which included tachycardia, heart palpitations, and fatigue, and led to discontinuation. Four patients treated with omaveloxolone (one at 40 mg and three at 160 mg) had increases in transaminases that were >3 times the upper limit of normal, but these subsequently resolved without intervention or discontinuation.

In the MOXIe trial, omaveloxolone was generally well-tolerated in patients with Friederich's ataxia. In Part 1 of the study there was a single discontinuation at the 40 mg dose due to a skin rash [10]. Adverse events were generally mild and most common were respiratory infections and nasopharyngitis. Some patients had increased aminotransferases without other signs of liver injury. In Part 2 of the study, transient, reversible increases in aminotransferases were also observed without evidence of liver injury. The most common adverse events were nausea, headache, and fatigue [1].
In the MOXIe trial extension up to 144 weeks, the safety profile was similar to what was seen in Parts I and 2 of the trial [11]. None of the severe adverse events were considered drug related. The most common treatment-emergent adverse events were increased ALT not accompanied by elevations in total bilirubin. Adverse events occurring in ≥10% of patients included headache, upper respiratory tract infection, nausea, fatigue, and diarrhea.
Over the course of the MOXIe trial, the most common adverse events that occurred in a higher proportion of omaveloxolone-treated patients, relative to placebo were elevated aminotransferases (37% omaveloxolone vs 2% placebo), headache (37% vs 25%), nausea (33% vs 13%), abdominal pain (29% vs 6%), fatigue (24% vs 14%), diarrhea (20% vs 10%) and musculoskeletal pain (20% vs 15%) [32] .
In the Phase I trial testing lotion supplemented with up to 3% omaveloxolone, the lotion was well tolerated and only one person in the highest dose group experienced minor redness and itching [18].

Omaveloxolone has not been clinically tested in patients over age 65, so it is unclear if the pharmacological profile is impacted by age [33].

Drug interactions: Omaveloxolone is primarily metabolized by CYP3A enzymes, with minor metabolism by CYP2C8 and CYP2J2 enzymes [33]. As a result, omaveloxolone should not be used in combination with strong CYP3A4 inhibitors. According to Drugs.com, there are 441 drugs that interact with omaveloxolone. The nine drugs with strong interactions include drospirenone, estradiol, ethinyl estradiol, etonogestrel, levonorgestrel, lumateperone, medroxyprogesterone, norethindrone, and norgestrel. Omaveloxolone may reduce the efficacy of some hormonal forms of birth control.

A Phase 1 clinical trial (NCT04008186) was conducted testing the potential interactions between omaveloxolone and a variety of substrates and inhibitors of metabolic enzymes and drug transporters, including Midazolam oral solution, Repaglinide 1 mg, Metformin 500 mg oral tablet, Rosuvastatin, Digoxin tablet, Gemfibrozil tablets, Itraconazole capsule, and Verapamil pill. However, the results have not been posted.

Sources and dosing:

Omaveloxolone (RTA-408) was developed by Reata Pharmaceuticals and its use in clinical trials was being sponsored by both Reata and AbbVie. In October 2019, Reata reacquired the rights to commercially develop omaveloxolone from AbbVie (Press release). It was granted Orphan Drug Status by the FDA in June 2017 for Friederichs's ataxia and received Fast Track Designation from the FDA in 2021. Omaveloxolone was approved for in patients ≥ 16 years old with Friedreich's ataxia in February 2023 (FDA Press release). It is being marketed under the trade name SKYCLARYS®. In July 2023, Reata was acquired by Biogen (Press release).

The therapeutic dose for Friederich's ataxia has been established at 150 mg/day (orally) in the form of three 50 mg capsules [32]. The capsules should be taken on an empty stomach, at least one hour prior to the consumption of food. Because plasma exposure of omaveloxolone is increased in patients with moderate to severe hepatic impairment (Child-Pugh class B and C), the recommended dose for these patients is 100 mg/day [33]. It is recommended that patients have liver function assessed prior to initiating treatment, and to have periodic assessments of liver enzyme levels and functional tests while taking omaveloxolone [32]. The therapeutic dose for the radiation protection lotion is projected to be 3%.

Research underway:

According to Clinicaltrials.gov, Friedreich ataxia patients in the Phase 2 MOXIe trial will continue to be monitored through 2024 (NCT02255435). Additionally, there are active clinical trials testing omaveloxolone in healthy subjects to determine the impact of a moderate CYP3A4 inducer on the pharmacokinetics of omaveloxolone (NCT05909644). Omaveloxolone is also being tested in healthy subjects to assess the effect of omaveloxolone on QTc Interval (NCT05927649).

Search terms:
Pubmed, Google: RTA-408 + (or omaveloxolone +) clinical trials, safety, neurodegeneration, neuroprotection, meta-analysis, cancer, aging, cardiovascular, mitochondria, Nrf2

Websites visited for Omaveloxolone:

- Clinicaltrials.gov
- Pubchem

- Drugs.com
- DrugBank.ca
- WebMD

References:

1. Lynch DR, Chin MP, Delatycki MB *et al.* (2021) Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study). *Annals of Neurology* **89**, 212-225https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.25934.

2. Yang B, Pan J, Zhang XN *et al.* (2023) NRF2 activation suppresses motor neuron ferroptosis induced by the SOD1(G93A) mutation and exerts neuroprotection in amyotrophic lateral sclerosis. *Neurobiology of disease* **184**, 106210https://pubmed.ncbi.nlm.nih.gov/37352984/.

3. Shekh-Ahmad T, Eckel R, Dayalan Naidu S *et al.* (2018) KEAP1 inhibition is neuroprotective and suppresses the development of epilepsy. *Brain* **141**, 1390-1403http://dx.doi.org/10.1093/brain/awy071.

4. Zhang L, Zhou Q, Zhou C-L (2021) RTA-408 protects against propofol-induced cognitive impairment in neonatal mice via the activation of Nrf2 and the inhibition of NF-κB p65 nuclear translocation. *Brain and Behavior* **11**, e01918https://onlinelibrary.wiley.com/doi/abs/10.1002/brb3.1918.

5. Yang C-C, Lin C-C, Jou M-J *et al.* (2019) RTA 408 Inhibits Interleukin-1β-Induced MMP-9 Expression via Suppressing Protein Kinase-Dependent NF-κB and AP-1 Activation in Rat Brain Astrocytes. *International Journal of Molecular Sciences* **20**, 2826https://www.mdpi.com/1422-0067/20/11/2826.

6. Hu L, Cao Y, Chen H *et al.* (2022) The Novel Nrf2 Activator Omaveloxolone Regulates Microglia Phenotype and Ameliorates Secondary Brain Injury after Intracerebral Hemorrhage in Mice. *Oxid Med Cell Longev* **2022**, 4564471https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8933082/.

7. Madsen KL, Buch AE, Cohen BH *et al.* (2020) Safety and efficacy of omaveloxolone in patients with mitochondrial myopathy. *MOTOR trial* **94**, e687-e698https://n.neurology.org/content/neurology/94/7/e687.full.pdf.

8. Zighan M, Arkadir D, Douiev L *et al.* (2022) Variable effects of omaveloxolone (RTA408) on primary fibroblasts with mitochondrial defects. *Frontiers in molecular biosciences* **9**, 890653https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9411646/.

9. Abeti R, Baccaro A, Esteras N *et al.* (2018) Novel Nrf2-Inducer Prevents Mitochondrial Defects and Oxidative Stress in Friedreich's Ataxia Models. *Frontiers in Cellular Neuroscience* **12**, 188http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6056642/.

10. Lynch DR, Farmer J, Hauser L *et al.* (2018) Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. *Ann Clin Transl Neurol* **6**, 15-26https://pubmed.ncbi.nlm.nih.gov/30656180

11. Lynch DR, Chin MP, Boesch S *et al.* (2023) Efficacy of Omaveloxolone in Friedreich's Ataxia: Delayed-Start Analysis of the MOXIe Extension. *Movement disorders : official journal of the Movement Disorder Society* **38**, 313-320https://pubmed.ncbi.nlm.nih.gov/36444905/.

12. Lynch DR, Goldsberry A, Rummey C *et al.* (2023) Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data. *Ann Clin Transl Neurol*https://pubmed.ncbi.nlm.nih.gov/37691319/.

13. Alexeev V, Lash E, Aguillard A *et al.* (2014) Radiation protection of the gastrointestinal tract and growth inhibition of prostate cancer xenografts by a single compound. *Molecular cancer therapeutics* **13**, 2968-2977http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4258451/.

14. Luginbuhl AJ, Hobelmann K, Rodin J *et al.* Synthetic Triterpenoid RTA-408: Limits Radiation Damage to Normal Tissue. *The Laryngoscope* **n/a**https://onlinelibrary.wiley.com/doi/abs/10.1002/lary.29930.

15. Luginbuhl AJ, Hobelmann K, Rodin J *et al.* (2022) Synthetic Triterpenoid RTA-408: Limits Radiation Damage to Normal Tissue. *Laryngoscope* **132**, 1196-1204https://pubmed.ncbi.nlm.nih.gov/34709651/.

16. Rabbani PS, Ellison T, Waqas B *et al.* (2018) Targeted Nrf2 activation therapy with RTA 408 enhances regenerative capacity of diabetic wounds. *Diabetes Research and Clinical Practice* **139**, 11-23https://doi.org/10.1016/j.diabres.2018.02.021.

17. Kuhn J, Sultan DL, Waqas B *et al.* (2020) Nrf2-activating Therapy Accelerates Wound Healing in a Model of Cutaneous Chronic Venous Insufficiency. *Plast Reconstr Surg Glob Open* **8**, e3006-e3006https://pubmed.ncbi.nlm.nih.gov/33299679

18. Reisman SA, Goldsberry AR, Lee C-YI *et al.* (2015) Topical application of RTA 408 lotion activates Nrf2 in human skin and is well-tolerated by healthy human volunteers. *BMC Dermatology* **15**, 10http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4501113/.

19. Creelan BC, Gabrilovich DI, Gray JE *et al.* (2017) Safety, pharmacokinetics, and pharmacodynamics of oral omaveloxolone (RTA 408), a synthetic triterpenoid, in a first-in-human trial of patients with advanced solid tumors. *OncoTargets and therapy* **10**, 4239-4250http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5587199/.

20. Tejera Nevado P, Tešan Tomić T, Atefyekta A *et al.* (2023) Synthetic oleanane triterpenoids suppress MYB oncogene activity and sensitize T-cell acute lymphoblastic leukemia cells to chemotherapy. *Frontiers in oncology* **13**, 1126354https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10106619/.

21. Cohen-Nowak AJ, Cohen AJ, Correia ED *et al.* (2022) Omaveloxolone attenuates squamous cell carcinoma growth and disease severity in an Epidermolysis Bullosa mouse model. *Experimental dermatology* **31**, 1083-1088https://pubmed.ncbi.nlm.nih.gov/35285087/.

22. Sun J, Li J-Y, Zhang L-Q *et al.* (2021) Nrf2 Activation Attenuates Chronic Constriction Injury-Induced Neuropathic Pain via Induction of PGC-1α-Mediated Mitochondrial Biogenesis in the Spinal Cord. *Oxidative Medicine and Cellular Longevity* **2021**, 9577874https://doi.org/10.1155/2021/9577874.

23. Chien J-Y, Chou Y-Y, Ciou J-W *et al.* (2021) The Effects of Two Nrf2 Activators, Bardoxolone Methyl and Omaveloxolone, on Retinal Ganglion Cell Survival during Ischemic Optic Neuropathy. *Antioxidants* **10**, 1466https://www.mdpi.com/2076-3921/10/9/1466.

24. Sun X, Xie Z, Hu B *et al.* (2020) The Nrf2 activator RTA-408 attenuates osteoclastogenesis by inhibiting STING dependent NF-κb signaling. *Redox Biology* **28**, 101309https://www.sciencedirect.com/science/article/pii/S2213231719307141.

25. Taylor EL, Collins JA, Gopalakrishnan P *et al.* (2023) Age and oxidative stress regulate Nrf2 homeostasis in human articular chondrocytes. *Osteoarthritis and cartilage* **31**, 1214-1223https://pubmed.ncbi.nlm.nih.gov/37160250/.

26. Jiang Z, Qi G, Lu W *et al.* (2022) Omaveloxolone inhibits IL-1β-induced chondrocyte apoptosis through the Nrf2/ARE and NF-κB signalling pathways in vitro and attenuates osteoarthritis in vivo. *Frontiers in pharmacology* **13**, 952950https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9551575/.

27. Reisman SA, Ferguson DA, Lee C-YI *et al.* (2020) Omaveloxolone and TX63682 are hepatoprotective in the STAM mouse model of nonalcoholic steatohepatitis. *Journal of Biochemical and Molecular Toxicology* **34**, e22526https://onlinelibrary.wiley.com/doi/abs/10.1002/jbt.22526.

28. Zhang J-h, Yang X, Chen Y-p *et al.* (2019) Nrf2 Activator RTA-408 Protects Against Ozone-Induced Acute Asthma Exacerbation by Suppressing ROS and γδT17 Cells. *Inflammation* **42**, 1843-1856https://doi.org/10.1007/s10753-019-01046-6.

29. Shrestha D, Massey N, Bhat SM *et al.* (2022) Nrf2 Activation Protects Against Organic Dust and Hydrogen Sulfide Exposure Induced Epithelial Barrier Loss and K. pneumoniae Invasion. *Frontiers in cellular and infection microbiology* **12**, 848773https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9062039/.

30. Boghdeh NA, McGraw B, Barrera MD *et al.* (2023) Inhibitors of the Ubiquitin-Mediated Signaling Pathway Exhibit Broad-Spectrum Antiviral Activities against New World Alphaviruses. *Viruses* **15**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10059822/.

31. Boghdeh NA, Risner KH, Barrera MD *et al.* (2022) Application of a Human Blood Brain Barrier Organ-on-a-Chip Model to Evaluate Small Molecule Effectiveness against Venezuelan Equine Encephalitis Virus. *Viruses* **14**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9786295/.

32. Lee A (2023) Omaveloxolone: First Approval. *Drugs* **83**, 725-729https://pubmed.ncbi.nlm.nih.gov/37155124/.

33. (2023) Omaveloxolone. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists* **80**, 789-791https://pubmed.ncbi.nlm.nih.gov/37137161/.