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 (RTA-408)

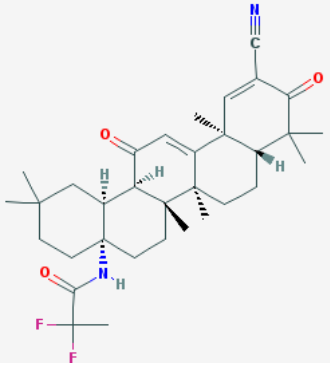
Evidence Summary

It may be useful to protect mitochondria against oxidative stress damage in pathological conditions, and reduce inflammation, but it's unclear if it can protect against age-related mitochondrial damage.

Neuroprotective Benefit: It may help protect against mitochondrial damage in neurons and preserve motor function. It may also mitigate neuroinflammation. Potential effects on cognition have not been established and more human studies are needed.

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: Used in clinical trials. Available from biological chemical suppliers for research, but not human, use.	**Dose**: 150 mg daily oral capsule (Friedreich's ataxia)	**Chemical formula:** $C_{33}H_{44}F_2N_2O_3$ **MW**: 554.723 g/mol  Source: Pubchem
Half-life: Range 9-24 hours	**BBB**: penetrant	
Clinical trials: One Phase 2 for mitochondrial myopathy (n=53), Phase 2/3 trial for Friedreich's ataxia (n=69, 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. It is currently being developed for Friedreich's ataxia.

Neuroprotective Benefit: It may help protect against mitochondrial damage in neurons and preserve motor function. It may also mitigate neuroinflammation. Potential effects on cognition have not been established and more human studies are needed.

Types of evidence

- 1 RCT assessing neurological function in Friedreich's ataxia
- 3 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:

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 [2]. 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 [3]. 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 primary neuroprotective 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-1ß [4]. It has not been established which cell types are the primary targets of omaveloxolone *in vivo*.

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 two 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 improve mitochondrial function in the absence of pathology or 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 [5]. 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.

Friedreich's ataxia: POTENTIAL 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)[6].

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 [7]. 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.

Based on the results from this study, Reata Pharmaceuticals has received Fast Track Designation from the FDA for the development of omaveloxolone for Friedreich's ataxia (Press release). They plan to file a New Drug Application (NDA) in the first quarter of 2022.

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 [8]. 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 [9]. 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 [10; 11].

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 [12], 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

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 [13]. 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.

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 [14]. 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 [15]. 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 [16]. 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.

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 [17]. 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 [18]. 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).

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 mechanisms of action 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) [13]. 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 [5]. 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 [7]. 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 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 [12].

Drug interactions: 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 and potential drug interactions have not been disclosed.

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 is only available to patients enrolled in clinical trials. It received Fast Track Designation from the FDA in 2021 and Reata will be seeking drug approval in 2022. It can be purchased for research, but not patient use, through biological chemical suppliers.

The therapeutic dose for Friedreich's ataxia has been established at 150 mg/day (orally). The therapeutic dose for the radiation protection lotion is projected to be 3%.

Research underway:

There are currently no active clinical trials for Omaveloxolone on Clinicaltrials.gov. Reata Pharmaceuticals is working with the FDA to seek approval for omaveloxolone in Friedreich's ataxia.

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
- DrugBank.ca

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