*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**

May be useful to protect mitochondria against oxidative stress damage in pathological conditions, particularly in the nervous system. Unclear if it can protect against age-related mitochondrial damage.

**Neuroprotective Benefit:** May help protect against mitochondrial damage in neurons. Human studies are needed.

**Aging and related health concerns:** 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:** Well tolerated with no major safety concerns based on Phase 1 and Phase 2 studies. Long-term safety profile needs to be determined.

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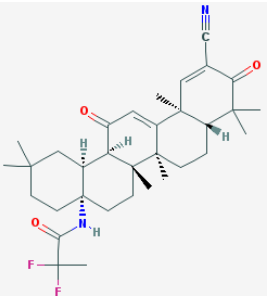
|---|---|---|
| **Availability**: Clinical trials. | **Dose**: 160 mg daily oral capsule (mitochondria protection) | **Chemical formula:** $C_{33}H_{44}F_2N_2O_3$<br>**MW**: 554.723 g/mol |
| **Half-life**: Range 9-24 hours | **BBB**: penetrant |  <br>Source: Pubchem |
| **Clinical trials**: Two Phase 2 for mitochondrial diseases (n=53, 69) show possible benefit. Phase 2 trials for cancer (n=41), radioprotection (n=187), and protection against cornea damage (n=304) are completed but have not published results. | **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 is being tested in clinical trials for mitochondrial diseases, cancer, and to protect against radiotherapy-induced skin damage and ophthalmic surgery induced corneal damage.

**Neuroprotective Benefit:** May help protect against mitochondrial damage in neurons. Human studies are needed.

*Types of evidence:*

- 1 laboratory study

There have been no studies in humans examining the neuroprotective effects of omaveloxolone. A single preclinical study showed evidence of neuroprotection in an epilepsy model. The mechanism of action involves preservation of mitochondria in the context of cellular stressors.

*Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?* None

*Human research to suggest benefits to patients with dementia*: None

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

**Epilepsy: Potential benefit (mice)**
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 [1]. 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.

*APOE4 interactions*: Unknown

**Aging and related health concerns:** 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:*

- 2 clinical trials (Phase 2 placebo-controlled RCTs)
- Numerous laboratory studies

**Mitochondria-associated diseases: Potential Benefit**

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 improve mitochondrial function in the absence of pathology or protect against age-related mitochondrial dysfunction.

**-Mitochondrial myopathy**

In a Phase 2 RCT (MOTOR NCT02255422) of 53 patients with mitochondrial myopathy (age 18-75) who received omaveloxolone at the therapeutic dose of 160 mg (n=10) there were no significant effects in the primary and secondary outcomes of peak work and the distance walked in 6 min walk test, respectively. However, in submaximal exercise testing, treated patients demonstrated a significant lowering of heart rate (p=0.01) and blood lactate (p=0.04), which are indicative of improved mitochondrial function. While this study was too small to provide reliable information about efficacy, these results suggest omaveloxolone may be useful in the treatment of mitochondriopathies.

-Friedreich's ataxia

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) [2].

In the Phase 2 range dosing part of a Phase2/3 RCT (MOXie NCT02255435) with Friedreich's ataxia patients, all doses significantly improved neurological function, as measured by the modified Friedreich's Ataxia Rating Scale (mFARS), from baseline (P<0.001). Measures of peak work were also improved from baseline (P=0.04) in patients without foot deformities (the presence of the deformity confounds the testing). However, neither of these effects was significant when compared to placebo. The Phase 3 part will be needed to determine whether omaveloxolone provides true clinical benefit for this mitochondrial disease.

Radiation damage: Potential benefit (mice)

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 [3]. 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).

In light of these positive preclinical results, omaveloxolone is now being developed as an adjunct for cancer patients receiving radiotherapy. A lotion containing 3% omaveloxolone has shown a good safety profile in healthy volunteers [4], 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: Unknown

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) non-small-cell lung carcinoma (NSCLC) or melanoma but did not prevent disease progression in this study [5]. However, the highest dose (15 mg) 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. While the results have not yet been made available (trial concluded May 2018), trial patients have been granted extended access to the drug, suggesting some patients may have benefited.

**Safety:** Well tolerated with no major safety concerns based on Phase 1 and Phase 2 studies. Long-term safety profile needs to be determined.

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

There have been no major safety concerns reported for Omaveloxolone. **All reported adverse events have been mild or moderate.** 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) [5]. Heart function was not negatively affected based on serial electrocardiography (ECG) and plasma B-type natriuretic peptide (BNP) levels.

In Phase 2 trials testing up to 160 mg in oral capsules, there were no reported safety issues and the most common adverse events relative to placebo were upper respiratory infections and nasopharyngitis (mild). One patient discontinued due to skin rash.

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 [4].

Potential drug interactions are unknown.

**Sources and dosing:**

Omaveloxolone (RTA-408) was developed by Reata Pharmaceuticals and its use in clinical trials is being sponsored by both Reata and AbbVie. 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 can be purchased for research, but not patient use, through biological chemical suppliers.

The therapeutic dose for mitochondrial protection has been established at 160 mg/day (orally). The therapeutic dose for the radiation protection lotion is projected to be 3%. The therapeutic dose for cancer has not yet been established/made public.

**Research underway:**

There are two active clinical trials. One is a Phase 1 trial (NCT03664453) testing the pharmacokinetics of omaveloxolone in healthy volunteers. The other is the Phase 3 part of the MOXie trial (NCT02255435) testing omaveloxolone in patients with Friederichs'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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