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Trends in Pharmacological Sciences | Drug of the Month

Omaveloxolone (Skyclarys™) for patients with Friedreich's ataxia

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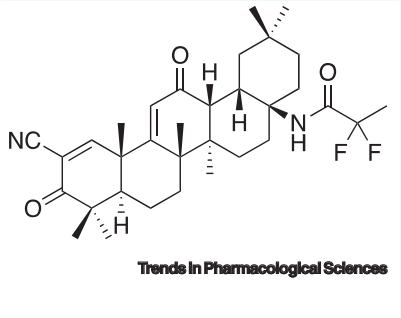
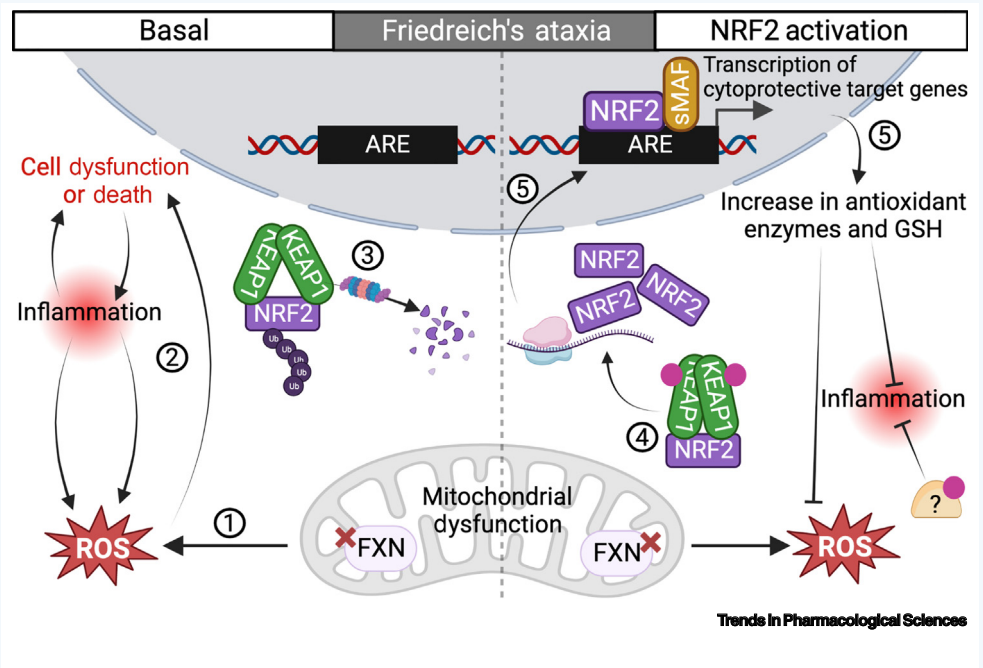


STRUCTURE: Omaveloxolone {N-[(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-2,2,6a,6b, 9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octa-decahydropicen-4a-yl]-2,2-difluoropropanamide} is a semisynthetic triterpenoid based on the natural product oleanolic acid. It contains a highly reactive cyanoenone functionality, which binds covalently and reversibly by Michael addition to cysteines in proteins, such as the cysteine-based sensor protein Kelch-like ECH-associated protein 1 (KEAP1). The molecular formula of omaveloxolone is $C_{33}H_{44}F_2N_2O_3$ and its molecular weight is 554.7 g/mol.



MECHANISM OF ACTION: The pathophysiology of Friedreich's ataxia is associated with an expansion of GAA repeats in the first intron of *FXN* encoding the small mitochondrial protein frataxin (FXN), which has a role in mitochondrial homeostasis and iron metabolism. FXN deficiency leads to impaired mitochondrial function and increased production of reactive oxygen species (ROS) (1), in turn causing inflammation with further ROS production, creating a vicious cycle that ultimately results in cellular dysfunction (2). Omaveloxolone is an inducer of a network of endogenous cytoprotective proteins regulated by transcription factor nuclear factor-erythroid 2 p45-related factor 2 (NRF2), the master regulator of cellular redox homeostasis. At basal state, the levels of NRF2 are low due to its continuous proteasomal degradation (3) mediated by KEAP1, a substrate adapter of a

NAME:
Omaveloxolone (also known as RTA-408); brand name is SKYCLARYS.

DRUG CLASS:
Omaveloxolone is the first and only FDA-approved drug for patients with Friedreich's ataxia. Omaveloxolone has received Orphan Drug, Fast Track, and Rare Pediatric Disease Designations from the FDA, and Orphan Drug Designation for the treatment of Friedreich's ataxia from the European Commission. It is currently not approved outside of the USA.

CLINICAL USE:
SKYCLARYS™ is approved in the USA by the FDA and is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older. The recommended dosage is 150 mg to be taken orally daily.

DEVELOPED BY:
Reata Pharmaceuticals.

ADVERSE EFFECTS:
Headache (37%), nausea (33%), diarrhea (20%), abdominal pain (29%), fatigue (24%), musculoskeletal pain (20%), vomiting (16%), oropharyngeal pain (18%), influenza (16%), muscle spasms (14%), back pain (13%), decreased appetite (12%), rash (10%). The most common laboratory abnormalities (occurring in 37% of patients) are elevated aspartate/alanine transaminases. In clinical trials, most effects diminished or stopped after 12 weeks of treatment.

TIMELINE:
2014–2020: Phase 1 trials (NCT02029716, NCT03664453, NCT04008186)

2014–present: Phase 2 trials (NCT02255435, NCT02029729, NCT02142959, NCT02128113, NCT03902002, NCT02255422)

February 2023: FDA approval for SKYCLARYS™ (omaveloxolone).

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Cullin-RING E3 ubiquitin ligase. Omaveloxolone (pink circle), via its cyanoenone functionality, binds to sensor cysteines (primarily C151) in KEAP1 and inactivates it (4). As a result, the newly synthesized NRF2 accumulates, forms a heterodimer with a small musculoaponeurotic fibrosarcoma (sMAF) protein, and induces transcription of its target genes by binding to the antioxidant response element (ARE) sequences in their regulatory regions. The NRF2-transcriptional network encompasses an array of broadly cytoprotective proteins (5), including those responsible for the biosynthesis of glutathione (GSH). Collectively, the NRF2 transcriptional targets counteract oxidative and inflammatory stress, and support proteostasis, mitochondrial function, and bioenergetics. Omaveloxolone also inhibits inflammation, in part via NRF2 (which inhibits transcription of proinflammatory genes) and, in part, due to its potential to bind to cysteines in proteins involved in inflammatory cascades (e.g., IKKβ, shown in beige).

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Declaration of interests

A.T. D.-K. is a member of the Scientific Advisory Board of Evgen Pharma and collaborates with GlaxoSmithKline and Reata Pharmaceuticals. S.D.N. has no interests to declare.

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