

RESEARCH MONOGRAPH . COMPOUND PROFILE

Omaveloxolone

A second-generation synthetic triterpenoid developed by Reata Pharmaceuticals as a potent activator of the Nrf2 cytoprotective pathway and the first FDA-approved pharmacotherapy for Friedreich ataxia, distinguished from earlier Nrf2 modulators by clinical validation in a neurodegenerative indication and a favorable therapeutic index at the registered oral dose.

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AUTHOR	Kodi <i>ac</i> biolabs Research
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ABSTRACT

Omaveloxolone (RTA 408; marketed as Skyclarys) is a semi-synthetic oleanane triterpenoid and potent activator of nuclear factor erythroid 2-related factor 2 (Nrf2) that received United States Food and Drug Administration approval in February 2023 as the first and, as of the date of this monograph, only pharmacotherapy indicated for the treatment of Friedreich ataxia in adults and adolescents aged 16 years and older. The compound operates through a dual mechanism: covalent modification of sensor cysteines (primarily Cys151) on the Kelch-like ECH-associated protein 1 (KEAP1) repressor, which stabilizes Nrf2 and permits its nuclear translocation and transcriptional activation of antioxidant response element (ARE)-driven cytoprotective genes; and direct inhibition of the nuclear factor kappaB (NF-kappaB) pro-inflammatory signaling cascade. These combined activities restore mitochondrial bioenergetics, elevate intracellular glutathione, induce heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1), and suppress inflammatory cytokine production in both cellular and animal models of oxidative stress and neurodegeneration.

The clinical development of omaveloxolone centered on the MOXIe program (NCT02255435), a two-part, randomized, double-blind, placebo-controlled trial conducted across 11 institutions in the United States, Europe, and Australia. In MOXIe Part 2, 103 patients with genetically confirmed Friedreich ataxia aged 16 to 40 years were randomized 1:1 to placebo or omaveloxolone 150 mg orally once daily for 48 weeks. The primary endpoint, change from baseline in the modified Friedreich Ataxia Rating Scale

(mFARS), demonstrated a statistically significant placebo-corrected difference of negative 2.40 points ($p = 0.014$), with omaveloxolone-treated patients showing neurological improvement (negative 1.55 points) against placebo-treated worsening (positive 0.85 points). Extension data and propensity-matched natural history comparisons have supported persistent benefit over four years of continuous treatment.

Pharmacokinetics are characterized by slow and variable oral absorption (median time to peak concentration 7 to 14 hours), high protein binding (97 percent), a large apparent volume of distribution (approximately 7361 liters), and a long terminal elimination half-life (mean 57 hours, range 32 to 90 hours). Metabolism is predominantly hepatic via cytochrome P450 3A4 (CYP3A4), with minor contributions from CYP2C8 and CYP2J2. Elimination is primarily through the hepatobiliary route and fecal excretion. A clinically significant food effect is present: coadministration with a high-fat meal increases peak plasma concentration (C_{max}) by approximately 350 percent with only a 15 percent increase in total exposure (AUC), necessitating fasted-state administration. Strong CYP3A4 inhibitors increase omaveloxolone exposure approximately 4-fold and require dose modification.

The principal adverse events in clinical trials were elevated hepatic aminotransferases (alanine aminotransferase elevation in 37 percent of patients, with 16 percent exceeding 5 times the upper limit of normal), headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain. The aminotransferase elevations have been attributed to enzyme induction rather than hepatocellular injury, as bilirubin and albumin levels remained within normal limits; however, periodic hepatic function

monitoring is required during treatment. Earlier clinical programs explored omaveloxolone in oncology (advanced solid tumors, melanoma adjunct to checkpoint inhibitors) and radiation dermatitis (topical formulation), though the Friedreich ataxia indication is the sole approved application.

This monograph documents the chemistry, synthesis, and structural class of omaveloxolone; the molecular pharmacology of the KEAP1-Nrf2-ARE axis and NF-kappaB inhibition; comprehensive pharmacokinetics including food effect, drug interactions, and special populations; the preclinical pharmacology across oxidative stress and mitochondrial dysfunction models; the clinical evidence base from the MOXIe program and oncology studies; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; the adverse event and safety profile; and a structured comparative assessment of five alternative Nrf2-modulating or Friedreich ataxia-relevant compounds (dimethyl fumarate, sulforaphane, bardoxolone methyl, idebenone, EPI-743) against omaveloxolone on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Omaveloxolone.

Marketed name: Skylarys (Biogen, formerly Reata Pharmaceuticals; United States, European Union, and other jurisdictions).

Development codes: RTA 408 (Reata Pharmaceuticals). The development code is the canonical identifier in the early pharmacology literature, oncology trial publications, and the preclinical characterization studies. The compound is also referenced in the medicinal chemistry literature as CDDO-DFPA (2-cyano-3,12-dioxo-28-noroleana-1,9(11)-dien-17-yl 2,2-difluoropropanamide), reflecting its structural relationship to the CDDO (2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid) triterpenoid series [1, 2].

Chemical Abstracts Service registry number: 1474034-05-3.

International Union of Pure and Applied Chemistry name: N-[(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,3,4,5,6,6a,7,8,8a,10,12a,14,14a,14b-tetradecahydropicen-4a-yl]-2,2-difluoropropanamide.

1.2 Structural class and chemistry

Omaveloxolone is a semi-synthetic oleanane triterpenoid belonging to the CDDO family of synthetic triterpenoids originally developed from oleanolic acid, a naturally occurring pentacyclic triterpenoid found in olive leaves, grape skins, and other plant sources. The compound is a second-generation derivative engineered for enhanced potency at the KEAP1-Nrf2 interface and improved pharmacokinetic properties relative to first-generation analogs such as bardoxolone methyl (CDDO-Me) and CDDO-imidazolide (CDDO-Im) [2, 3].

Molecular formula: C₃₃H₄₄F₂N₂O₃.

Molecular weight: 554.72 g/mol.

Physical properties: White to off-white crystalline powder. The compound is practically insoluble in water and freely soluble in dimethyl sulfoxide and organic solvents. The low aqueous solubility is a determinant of the dissolution-limited oral absorption and the pronounced food effect observed in clinical pharmacokinetic studies [4].

Key structural features: The cyanoenone functionality on the A ring is the pharmacophore responsible for covalent interaction with KEAP1 sensor cysteines. The difluoropropanamide group at the C-17 position differentiates omaveloxolone from bardoxolone methyl (which carries a methyl ester at C-28) and contributes to the distinct pharmacokinetic and safety profile. The pentacyclic oleanane scaffold provides the structural rigidity necessary for selective interaction with the KEAP1 Kelch domain [2, 5].

1.3 Synthesis

The synthesis of omaveloxolone proceeds from oleanolic acid through a series of oxidative and functional group transformations that install the cyanoenone pharmacophore on the A ring and the difluoropropanamide substituent at the C-17 nitrogen. The synthetic route involves: (1) oxidation and ring modification of the oleanolic acid A ring to introduce the 1-en-3-one system; (2) cyanation at C-2 to generate the alpha,beta-unsaturated cyanoenone; (3) oxidative modification of the C ring to install the C-12 ketone; (4) functional group manipulation at C-17 to introduce the amine; and (5) acylation with 2,2-difluoropropanoyl chloride to yield the difluoropropanamide [5, 6]. The compound is synthesized at pharmaceutical scale with high-performance liquid chromatography purity exceeding 98 percent. The synthetic complexity is moderate for the triterpenoid class; the cyanoenone installation is the most technically demanding step and requires careful control of reaction conditions to avoid over-oxidation or epimerization at adjacent stereocenters.

2. Abstract

Omaveloxolone (RTA 408; Skyclarys) is a semi-synthetic oleanane triterpenoid that activates the Nrf2 cytoprotective transcription factor through covalent modification of KEAP1 sensor cysteines, stabilizing Nrf2 for nuclear translocation and transcriptional activation of antioxidant response element (ARE)-driven genes. The compound simultaneously inhibits NF-kappaB-mediated inflammatory signaling. These dual activities produce a coordinated cellular response that elevates glutathione biosynthesis, induces phase II detoxification enzymes (HO-1, NQO1, glutathione S-transferases), enhances mitochondrial bioenergetics, and suppresses pro-inflammatory cytokine production [1, 2, 7].

The compound was approved by the United States Food and Drug Administration in February 2023 as the first pharmacotherapy for Friedreich ataxia, a progressive neurodegenerative disease caused by homozygous GAA trinucleotide repeat expansion in the frataxin (FXN) gene, resulting in frataxin protein deficiency, mitochondrial iron accumulation, oxidative damage, and progressive neurological and cardiac dysfunction [8, 9]. The rationale for Nrf2 activation in Friedreich ataxia is the observation that frataxin deficiency impairs Nrf2 signaling, producing a state of chronic oxidative vulnerability that is partially correctable by pharmacological Nrf2 stabilization [7, 10].

The pivotal MOXie Part 2 trial demonstrated that omaveloxolone 150 mg daily for 48 weeks produced a statistically significant improvement in neurological function as measured by the mFARS, with a placebo-corrected difference of negative 2.40 points ($p = 0.014$) [8]. Extension data have shown persistent benefit over four years [11]. The compound is administered orally in the fasted state at 150 mg once daily (three 50-mg capsules), with dose reduction to 100 mg for moderate hepatic impairment.

Earlier clinical programs evaluated omaveloxolone in oncology (advanced solid tumors in the DISCOVER trial, melanoma adjunct to checkpoint inhibitors in the REVEAL trial) and in radiation dermatitis prevention (topical formulation in the PRIMROSE trial), though these indications did not advance to registration [12, 13].

3. Discovery and Development History

3.1 Origin of the CDDO triterpenoid series

The synthetic triterpenoid series from which omaveloxolone derives originated in the laboratory of Michael Sporn and colleagues at Dartmouth Medical School in the late 1990s. The foundational compound, CDDO (2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid), was designed through systematic chemical modification of oleanolic acid to create a potent inducer of phase II cytoprotective enzymes and inhibitor of inflammatory mediators [14]. Structure-activity studies demonstrated that the introduction of the cyanoenone functionality on the A ring dramatically enhanced Nrf2 activation potency, with CDDO and its early derivatives (CDDO-Me, CDDO-Im, CDDO-EA, CDDO-TFEA) showing nanomolar potency for induction of NQO1 in murine hepatoma cells [14, 15].

3.2 Development of omaveloxolone

Reata Pharmaceuticals, founded in 2002, advanced the CDDO triterpenoid series through systematic medicinal chemistry optimization aimed at improving the therapeutic index. Bardoxolone methyl (CDDO-Me, RTA 402), the first clinical candidate from this series, entered development for chronic kidney disease and demonstrated significant improvements in estimated glomerular filtration rate in Phase 2 (the BEAM trial) [16]. However, the subsequent Phase 3 BEACON trial in patients with type 2 diabetes and stage 4 chronic kidney disease was terminated in October 2012 due to excess serious adverse events, including heart failure and cardiovascular mortality, in the bardoxolone methyl arm [17]. The cardiovascular safety signal was attributed in part to fluid retention and endothelin pathway effects specific to bardoxolone methyl.

Omaveloxolone was designed as a next-generation CDDO analog with structural modifications intended to preserve Nrf2 activation potency while mitigating the cardiovascular and fluid-retention liabilities observed with bardoxolone methyl. The difluoropropanamide substitution at C-17 (replacing the C-28 methyl ester of bardoxolone methyl) altered the physicochemical properties, tissue distribution,

and off-target pharmacology of the molecule [2, 5]. Reata advanced omaveloxolone into clinical development beginning in 2013, with initial programs in oncology and Friedreich ataxia.

3.3 Clinical development in Friedreich ataxia

The MOXIe program (NCT02255435) was initiated in 2014 as a two-part clinical trial. Part 1 was a dose-escalation study evaluating omaveloxolone at 2.5, 5, 10, 20, 40, 80, 150, and 300 mg daily in patients with Friedreich ataxia, which identified 150 mg as the optimal dose based on pharmacodynamic biomarker responses and tolerability [18]. Part 2 was a randomized, double-blind, placebo-controlled, 48-week efficacy study at the 150 mg dose [8].

The FDA granted omaveloxolone Fast Track designation in November 2017, Orphan Drug designation, and subsequently approved the compound on February 28, 2023, under the brand name Skyclarys [9]. The European Medicines Agency (EMA) granted conditional marketing authorization in February 2024. In October 2023, Biogen completed the acquisition of Reata Pharmaceuticals for approximately \$7.3 billion, bringing Skyclarys into the Biogen neuroscience portfolio [19].

3.4 Oncology and dermatology programs

Parallel clinical programs explored omaveloxolone outside the Friedreich ataxia indication. The DISCOVER trial (NCT02029729) was a Phase 1 dose-escalation study of oral omaveloxolone (2.5 to 300 mg daily) in patients with advanced solid tumors, predominantly non-small-cell lung carcinoma and melanoma [12]. The trial established safety and pharmacokinetic parameters but did not demonstrate objective tumor responses. The REVEAL trial (NCT02259231) evaluated oral omaveloxolone as an adjunct to ipilimumab or nivolumab in patients with stage 3 or 4 metastatic melanoma. The PRIMROSE trial (NCT02142959) tested a topical omaveloxolone lotion (0.5 percent and 3 percent formulations) for prevention of radiation dermatitis in breast cancer patients undergoing radiation therapy [13]. None of these programs advanced to registration.

4. Molecular Pharmacology

4.1 The KEAP1-Nrf2-ARE signaling axis

Under basal conditions, the transcription factor Nrf2 is maintained at low intracellular levels through continuous proteasomal degradation mediated by the KEAP1-Cullin 3 (CUL3) E3 ubiquitin ligase complex. KEAP1 functions as a substrate adaptor that binds Nrf2 through the DLG and ETGE motifs in the Neh2 domain and presents it for polyubiquitination and subsequent 26S proteasomal degradation. This constitutive turnover maintains Nrf2 half-life at approximately 15 to 20 minutes under unstressed conditions [20].

Omaveloxolone activates Nrf2 by covalently modifying sensor cysteine residues on KEAP1, primarily Cys151 in the BTB domain, through a Michael addition reaction between the electrophilic cyanoenone functionality of the triterpenoid A ring and the thiolate side chain of the cysteine [2, 20]. This covalent modification induces a conformational change in KEAP1 that disrupts the productive geometry of the KEAP1-CUL3 complex, preventing Nrf2 ubiquitination without preventing KEAP1-Nrf2 binding. The result is stabilization and nuclear accumulation of Nrf2, which heterodimerizes with small Maf proteins and binds to ARE sequences in the promoter regions of cytoprotective target genes [20, 21].

4.2 Nrf2 transcriptional targets

The Nrf2-driven transcriptional program activated by omaveloxolone includes: glutamate-cysteine ligase catalytic and modifier subunits (GCLC, GCLM), the rate-limiting enzymes in glutathione biosynthesis; heme oxygenase-1 (HMOX1/HO-1), which catalyzes the degradation of free heme to carbon monoxide, biliverdin, and iron; NAD(P)H quinone dehydrogenase 1 (NQO1), a two-electron reductase that detoxifies quinones; glutathione S-transferases (GSTA1, GSTM1, GSTP1); thioredoxin reductase 1 (TXNRD1); sulfiredoxin 1 (SRXN1); and multiple members of the multidrug resistance-associated protein family involved in cellular export of conjugated metabolites [7, 20, 21].

The net effect of this transcriptional program is a coordinated elevation of the cellular antioxidant and detoxification capacity, including increased intracellular glutathione pools, enhanced capacity for reactive oxygen species neutralization, improved mitochondrial electron transport chain function, and augmented capacity for clearance of damaged proteins and lipids.

4.3 NF-kappaB inhibition

Independent of the Nrf2 activation mechanism, omaveloxolone directly inhibits the NF-kappaB pro-inflammatory signaling pathway. The mechanism involves inhibition of IkappaB kinase beta (IKKbeta) through interaction with a reactive cysteine (Cys179) in the activation loop, preventing phosphorylation and degradation of the IkappaB inhibitory protein and thereby blocking nuclear translocation of the p65/p50 NF-kappaB heterodimer [2, 14]. The downstream consequence is suppression of NF-kappaB-driven transcription of pro-inflammatory cytokines (tumor necrosis factor alpha, interleukin-1 beta, interleukin-6), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and matrix metalloproteinases.

The dual Nrf2 activation and NF-kappaB inhibition produces a coordinated anti-inflammatory and cytoprotective pharmacological profile that is relevant to the pathophysiology of Friedreich ataxia, in which frataxin deficiency produces both oxidative vulnerability and low-grade inflammatory activation.

4.4 Relevance to Friedreich ataxia pathophysiology

Friedreich ataxia is caused by homozygous GAA trinucleotide repeat expansion in the first intron of the FXN gene, producing transcriptional silencing and deficiency of the mitochondrial protein frataxin. Frataxin deficiency impairs iron-sulfur cluster biogenesis, leading to mitochondrial iron accumulation, reactive oxygen species overproduction, impaired electron transport chain function (particularly complexes I, II, and III), and reduced cellular ATP production. The tissues most severely affected are dorsal root ganglia, cerebellar dentate nucleus, and cardiac myocytes, reflecting their high oxidative metabolic demand [22, 23].

Critically, frataxin deficiency also impairs Nrf2 signaling. Studies in Friedreich ataxia patient-derived cells and in frataxin-knockdown models have demonstrated reduced Nrf2 protein levels, decreased ARE-driven gene expression, and diminished glutathione pools [7, 10]. The pharmacological restoration of Nrf2 activity by

omaveloxolone therefore addresses a specific molecular deficit in the disease, rather than providing a nonspecific antioxidant effect. In frataxin-deficient cells, omaveloxolone treatment has been shown to restore glutathione levels, reduce mitochondrial superoxide production, and improve mitochondrial membrane potential and ATP generation [7, 10, 24].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Following oral administration of omaveloxolone 150 mg in the fasted state, absorption is slow and variable. The median time to peak plasma concentration (T_{max}) ranges from 7 to 14 hours postdose, reflecting the dissolution-limited absorption of this poorly water-soluble compound. Pharmacokinetics are approximately dose-proportional over the studied range of 2.5 to 300 mg [4, 12, 18].

A clinically significant and atypical food effect has been characterized: coadministration with a high-fat meal increases C_{max} by approximately 350 percent with only a 15 percent increase in AUC [4, 25]. Physiologically based biopharmaceutics modeling has attributed this effect to enhanced bile salt solubilization in the fed state, which accelerates dissolution and absorption in the upper gastrointestinal tract, increasing susceptibility to presystemic CYP3A4-mediated gut extraction. The paradoxical dissociation of C_{max} and AUC effects is attributable to the shift in absorption site from the distal intestine (fasted) to the proximal intestine (fed), where first-pass extraction is more efficient [25]. Because the safety profile was established in fasted-state dosing, the prescribing information requires administration at least one hour before or two hours after a meal.

The predicted mean steady-state C_{max} following 150 mg once daily in the fasted state in patients with Friedreich ataxia is approximately 71.5 ng/mL [4].

5.2 Distribution

Omaveloxolone has a large apparent volume of distribution of approximately 7361 liters (approximately 105 L/kg for a 70-kg individual), indicating extensive tissue partitioning. Plasma protein binding is approximately 97 percent [4]. The compound distributes into peripheral tissues including skeletal muscle, cardiac tissue, and the central nervous system, consistent with the therapeutic activity in neurodegenerative and cardiac manifestations of Friedreich ataxia.

5.3 Metabolism

Omaveloxolone is metabolized predominantly in the liver by CYP3A4, with minor contributions from CYP2C8 and CYP2J2. Two major plasma metabolites (each exceeding 10 percent of total plasma radioactivity) have been identified: 1,2-dihydro-30-COOH omaveloxolone (M22) and 1,2-dihydro-29-OH omaveloxolone (M17). Both metabolites are pharmacologically inactive at clinically relevant concentrations [4, 26].

The CYP3A4 dependence is the principal source of drug-drug interaction liability. Coadministration with the strong CYP3A4 inhibitor itraconazole increased omaveloxolone C_{max} and AUC by approximately 3-fold and 4-fold, respectively [26]. The prescribing information recommends avoidance of strong CYP3A4 inhibitors; if unavoidable, the omaveloxolone dose should be reduced to 50 mg daily. Moderate CYP3A4 inhibitors produce smaller but clinically relevant exposure increases. Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St. John's wort) are expected to reduce omaveloxolone exposure and may compromise efficacy.

Omaveloxolone is also an inhibitor of CYP3A4, CYP2C8, and the efflux transporter breast cancer resistance protein (BCRP) *in vitro*; potential clinical interactions with sensitive substrates of these enzymes and transporters should be considered [26].

5.4 Elimination

The mean terminal elimination half-life of omaveloxolone is 57 hours (range 32 to 90 hours), supporting once-daily dosing. Elimination occurs primarily through the hepatobiliary route, with fecal excretion as the predominant elimination pathway. Omaveloxolone is the major component in feces, suggesting that hepatobiliary excretion of parent compound, rather than metabolic clearance, is a substantial contributor to elimination. Renal excretion is a minor elimination pathway [4].

5.5 Routes of administration

The approved route of administration is oral. Omaveloxolone is supplied as 50 mg hard gelatin capsules for oral administration. The recommended dose is 150 mg (three capsules) taken once daily in the fasted state. A topical lotion formulation (0.5 percent and 3 percent) was developed and tested in the PRIMROSE radiation dermatitis trial but is not commercially available [13].

5.6 Special populations

Hepatic impairment: In subjects with moderate hepatic impairment (Child-Pugh Class B), omaveloxolone clearance is reduced and plasma exposure is increased. The recommended dose in moderate hepatic impairment is 100 mg daily, with further reduction to 50 mg if adverse reactions occur. Omaveloxolone has not been studied in severe hepatic impairment (Child-Pugh Class C) and is not recommended in this population [4].

Renal impairment: No dose adjustment is required for mild or moderate renal impairment. Omaveloxolone has not been studied in severe renal impairment or in dialysis patients [4].

Pediatric: The compound is approved for patients aged 16 years and older. Safety and efficacy have not been established in patients younger than 16 years.

Pregnancy: Animal reproductive toxicity studies have demonstrated adverse developmental effects at exposures below the human exposure at the recommended dose. Omaveloxolone may cause fetal harm; pregnancy testing is recommended before initiation of treatment, and effective contraception should be used during treatment and for 28 days after the last dose [4].

6. Preclinical Pharmacology

6.1 In vitro pharmacology

In cellular assays, omaveloxolone is a potent inducer of Nrf2-dependent gene expression. The concentration required for doubling of NQO1 activity (CD value) in murine hepatoma Hepa1c1c7 cells is in the low nanomolar range, placing omaveloxolone among the most potent synthetic Nrf2 activators characterized [2, 14]. In frataxin-deficient patient-derived fibroblasts, omaveloxolone treatment restored glutathione levels, reduced mitochondrial superoxide production, and improved mitochondrial membrane potential at concentrations of 10 to 100 nanomolar [7, 10].

In primary fibroblasts from patients with mitochondrial complex I deficiency, mitochondrial cytochrome oxidase deficiency, and Parkinson disease, omaveloxolone variably decreased reactive oxygen species production, significantly increased mitochondrial mass and mitochondrial DNA content, and increased maximal oxygen consumption rates in most cell lines studied [24]. The variability in response across different mitochondrial defect genotypes suggests that the therapeutic benefit of Nrf2 activation is partly dependent on residual mitochondrial function.

6.2 In vivo pharmacology

In a nonhuman primate pharmacokinetic and pharmacodynamic study, oral omaveloxolone produced dose-dependent increases in Nrf2 target gene expression (NQO1, HMOX1, GCLC) in peripheral blood mononuclear cells, confirming systemic Nrf2 activation at pharmacologically relevant oral doses [27].

In the conditional frataxin knockout mouse model of Friedreich ataxia, omaveloxolone preserved cardiac function, reduced oxidative stress markers, and extended survival relative to vehicle-treated controls. Importantly, omaveloxolone, but not dimethyl fumarate, improved cardiac function in Friedreich ataxia mice with severe cardiomyopathy, suggesting that the potency and tissue distribution of the triterpenoid Nrf2 activator confer therapeutic advantages over the fumarate class in the cardiac manifestation of the disease [28].

In hepatic ischemia-reperfusion injury models, omaveloxolone attenuated liver damage, reduced oxidative stress markers, decreased neutrophil infiltration, and inhibited apoptosis through activation of the Nrf2/HO-1 signaling pathway [29].

In the G93A SOD1 mouse model of amyotrophic lateral sclerosis, structurally related CDDO analogs (CDDO-EA and CDDO-TFEA) potentially activated Nrf2 in the central nervous system, induced Nrf2 target gene expression, suppressed NF-kappaB target genes, and induced genes associated with mitochondrial biogenesis [15].

6.3 Oncology preclinical pharmacology

Omaveloxolone has demonstrated antiproliferative activity in multiple cancer cell lines, with mechanisms including downregulation of the cell cycle regulator CDC20, inhibition of STAT3 signaling, and induction of apoptosis [30]. In glioblastoma cell lines, omaveloxolone suppressed cell growth and caused cell cycle arrest through CDC20 downregulation both in vitro and in vivo xenograft models [30]. These preclinical oncology activities supported the clinical exploration in the DISCOVER and REVEAL trials, though the clinical antitumor activity did not meet thresholds for further oncology development.

7. Clinical Evidence Base

7.1 MOXIe Part 1: Dose-finding

MOXIe Part 1 was an open-label, dose-escalation study evaluating omaveloxolone at eight dose levels (2.5, 5, 10, 20, 40, 80, 150, and 300 mg daily) in patients with Friedreich ataxia aged 16 to 40 years [18]. The study established 150 mg as the recommended dose based on: (1) dose-dependent pharmacodynamic biomarker responses (suppression of urinary 8-hydroxy-2-deoxyguanosine, elevation of ferritin); (2) plateau of the mFARS improvement signal at the 150 mg and 300 mg dose levels; and (3) acceptable tolerability at 150 mg with increasing aminotransferase elevations at 300 mg. The study also provided the initial safety database and pharmacokinetic characterization that informed Part 2 dosing [18].

7.2 MOXIe Part 2: Pivotal efficacy trial

MOXIe Part 2 was a randomized, double-blind, placebo-controlled, parallel-group trial conducted at 11 sites in the United States, Europe, and Australia. A total of 103 patients with genetically confirmed Friedreich ataxia (homozygous GAA repeat expansion), aged 16 to 40 years, with baseline mFARS scores of 20 to 80, were randomized 1:1 to omaveloxolone 150 mg daily or matching placebo for 48 weeks [8].

The primary efficacy endpoint was the change from baseline to Week 48 in the mFARS total score. Omaveloxolone-treated patients showed a mean change of negative 1.55 points (standard error 0.69), indicating neurological improvement, while placebo-treated patients showed a mean change of positive 0.85 points (standard error 0.64), indicating worsening. The placebo-corrected difference was negative 2.40 points (standard error 0.96; $p = 0.014$) [8].

Secondary endpoints, including individual mFARS subscores (upper limb, lower limb, upright stability, bulbar) and the patient-reported Activities of Daily Living score, showed directionally consistent but not uniformly statistically significant trends. Post hoc analyses demonstrated that the treatment effect was largely driven by improvements in upper limb coordination and upright stability subscores [8, 9].

7.3 Extension data and long-term outcomes

Patients completing MOXIe Part 2 were eligible to enter an open-label extension study in which all patients received omaveloxolone 150 mg daily. A delayed-start analysis comparing patients who received omaveloxolone from randomization (early-start group) to patients who transitioned from placebo to omaveloxolone at Week 48 (delayed-start group) demonstrated that early initiation of treatment conferred persistent advantage over delayed initiation, with the early-start group maintaining better mFARS scores through at least 144 weeks of follow-up [11].

A propensity-matched comparison of omaveloxolone-treated patients to Friedreich ataxia natural history data from the Friedreich Ataxia Clinical Outcome Measures Study (FA-COMS) demonstrated that omaveloxolone-treated patients showed significantly less neurological deterioration over time compared to propensity-matched untreated controls, supporting a disease-modifying effect rather than symptomatic benefit alone [31].

Long-term data through four years of continuous treatment have shown persistent slowing of disease progression, with omaveloxolone-treated patients maintaining functional status that would be expected to have declined substantially based on natural history projections [11, 31].

7.4 Oncology clinical studies

The DISCOVER trial (NCT02029729) was a Phase 1 first-in-human study of oral omaveloxolone in patients with advanced solid tumors. Doses of 2.5 to 300 mg daily were evaluated in 43 patients. The compound was well tolerated, and pharmacokinetic and pharmacodynamic parameters were established. No objective tumor responses were observed, though stable disease was reported in a subset of patients. The trial was not advanced to Phase 2 for oncology [12].

The REVEAL trial (NCT02259231) evaluated oral omaveloxolone (up to 100 mg daily) as an adjunct to ipilimumab or nivolumab in patients with unresectable stage 3 or 4 melanoma. The rationale was that Nrf2 activation in the tumor microenvironment could enhance the efficacy of immune checkpoint inhibitors by reducing oxidative stress-mediated T-cell dysfunction. Results have not been published in full, and the program was not advanced [13].

7.5 Radiation dermatitis

The PRIMROSE trial (NCT02142959) evaluated topical omaveloxolone lotion (0.5 percent and 3 percent) versus vehicle in breast cancer patients undergoing adjunctive radiation therapy. The trial aimed to determine whether topical Nrf2 activation could prevent or mitigate radiation-induced skin injury. Results have not been published as a full peer-reviewed report, and the topical formulation was not advanced to registration [13].

8. Sourcing and Quality Verification

Pharmaceutical-grade omaveloxolone is available commercially as Skyclarys (Biogen) in 50 mg hard gelatin capsules. The marketed formulation is the regulatory-grade reference material for clinical and clinical-research applications.

Research-grade omaveloxolone is supplied by multiple chemical and pharmaceutical research suppliers (Selleck Chemicals, MedChemExpress, Cayman Chemical, Tocris, ChemScene, Smolecule, InvivoChem, and others) at greater than 98 percent purity by HPLC. Supply is available in milligram to gram quantities as the free base. Pricing is moderate for a synthetic triterpenoid, typically in the range of \$100 to \$500 per 50 mg of research-grade material at the time of monograph preparation, with lower per-milligram pricing at larger quantities.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (555.72 for the protonated molecular ion $[M+H]^+$)
- Proton and carbon-13 nuclear magnetic resonance spectroscopy confirmation of structural identity, with attention to the diagnostic cyanoenone and difluoropropanamide resonances
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography for common synthesis solvents

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade omaveloxolone market is well established, and commercial suppliers are generally reliable; however, lot-to-lot variability in residual solvents and water content can affect dissolution behavior in vitro and should be characterized on receipt.

9. Reconstitution and Handling

Omaveloxolone is practically insoluble in water. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM to prepare stock solutions. DMSO stock solutions are stable at negative 20 degrees Celsius for at least 6 months when protected from light and stored in tightly sealed containers with minimal headspace. The final DMSO concentration in cell culture experiments should be maintained at or below 0.1 percent (v/v) to avoid solvent cytotoxicity.

For in vivo animal studies, omaveloxolone has been formulated in various vehicles including sesame oil, corn oil, methylcellulose suspensions, and polyethylene glycol-based formulations. The choice of vehicle affects oral bioavailability due to the compound's low aqueous solubility and dissolution-limited absorption. Lipid-based vehicles generally produce more consistent oral exposure than aqueous suspensions [27].

The solid compound should be stored at negative 20 degrees Celsius or at 2 to 8 degrees Celsius, protected from light and moisture. At room temperature in dry conditions, the compound is stable for at least 12 months based on supplier stability data. The crystalline powder is not hygroscopic and does not require desiccation under standard laboratory storage conditions.

For the pharmaceutical formulation (Skyclarys capsules), storage at 20 to 25 degrees Celsius (68 to 77 degrees Fahrenheit) is recommended, with excursions permitted to 15 to 30 degrees Celsius. The capsules should be stored in the original container with the desiccant canister to protect from moisture [4].

10. Stack Interactions and Combinations

Omaveloxolone interacts with several drug classes through its CYP3A4-mediated metabolism, its inhibition of CYP3A4, CYP2C8, and BCRP, and its pharmacological effects on hepatic enzyme induction. Investigators conducting research with omaveloxolone in combination regimens should consider the following interactions:

CYP3A4 inhibitors: Strong CYP3A4 inhibitors (itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir, cobicistat, grapefruit juice) increase omaveloxolone exposure approximately 3- to 4-fold. Concurrent use requires dose reduction to 50 mg daily or avoidance. Moderate CYP3A4 inhibitors (erythromycin, diltiazem, verapamil, fluconazole, aprepitant) produce smaller but clinically relevant increases and warrant monitoring [4, 26].

CYP3A4 inducers: Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort) are expected to reduce omaveloxolone exposure substantially and may compromise therapeutic efficacy. Concurrent use should be avoided when possible [4].

CYP3A4 substrates: Omaveloxolone inhibits CYP3A4 and may increase plasma concentrations of sensitive CYP3A4 substrates (midazolam, simvastatin, triazolam, cyclosporine, tacrolimus, sirolimus). Dose adjustments of the coadministered CYP3A4 substrate may be necessary [26].

CYP2C8 substrates: Omaveloxolone inhibits CYP2C8 and may increase exposure to CYP2C8 substrates (repaglinide, paclitaxel, cerivastatin, rosiglitazone) [26].

BCRP substrates: Omaveloxolone inhibits BCRP and may increase plasma concentrations of BCRP substrates (rosuvastatin, sulfasalazine, topotecan) [26].

Hormonal contraceptives: Omaveloxolone may reduce the efficacy of hormonal contraceptives through CYP3A4 induction at steady state. Additional or alternative contraceptive methods should be considered [4].

Idebenone and other antioxidants: Combination of omaveloxolone with idebenone (a synthetic analog of coenzyme Q10 used off-label in some Friedreich ataxia populations) has not been formally studied. The pharmacological rationale for combination is uncertain; both compounds target mitochondrial oxidative stress through different mechanisms, but the clinical benefit of combination over monotherapy is uncharacterized.

Hepatotoxic agents: Given the aminotransferase elevation signal with omaveloxolone, concurrent use with other potentially hepatotoxic agents should be approached with appropriate hepatic function monitoring.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events reported in the MOXIe clinical program and in post-marketing surveillance are:

- Elevated hepatic aminotransferases: ALT elevations were observed in 37 percent of omaveloxolone-treated patients, with 16 percent exceeding 5 times the upper limit of normal. AST elevations occurred at similar frequency. The elevations have been attributed to enzyme induction rather than hepatocellular injury, as serum bilirubin and albumin remained within normal limits. Over the first year of treatment, 56.6 percent of patients had at least one transaminase value above the upper limit of normal. Most elevations were transient, occurring in the first 12 to 16 weeks of treatment, and resolved with continued therapy or dose modification [4, 8, 32].
- Headache (approximately 20 to 25 percent)
- Nausea (approximately 15 to 20 percent)
- Abdominal pain (approximately 15 to 20 percent)
- Fatigue (approximately 15 to 20 percent)
- Diarrhea (approximately 10 to 15 percent)
- Musculoskeletal pain (approximately 10 to 15 percent)

11.2 Hepatic monitoring requirements

The FDA-approved prescribing information requires measurement of serum transaminases (ALT, AST) and total bilirubin before initiation of treatment, monthly for the first 12 months, and periodically thereafter. If ALT or AST elevation exceeds 5 times the upper limit of normal, treatment should be withheld until values return to below 3 times the upper limit of normal, and the dose should be reduced. If ALT or AST exceeds 10 times the upper limit of normal or if elevation is accompanied by clinical symptoms of liver injury or bilirubin elevation exceeding 2 times the upper limit of normal, permanent discontinuation is recommended [4].

11.3 Discontinuation rates

In the first year of postmarketing clinical experience, 21 of 236 patients (8.9 percent) permanently discontinued omaveloxolone. The most common reasons for discontinuation were gastrointestinal adverse events, fatigue, and aminotransferase elevations. The majority of adverse events were mild to moderate in severity [32].

11.4 Cardiovascular safety

Unlike bardoxolone methyl, which demonstrated excess cardiovascular serious adverse events (including heart failure and mortality) in the BEACON trial in patients with chronic kidney disease and type 2 diabetes, omaveloxolone has not produced a cardiovascular safety signal in the Friedreich ataxia clinical program [8, 17]. A thorough QT study in healthy volunteers demonstrated that a supratherapeutic dose of omaveloxolone did not produce clinically significant QTc prolongation [33]. The difference in cardiovascular safety between omaveloxolone and bardoxolone methyl is attributed to structural differences (the difluoropropanamide versus methyl ester substituent) and to the younger, non-diabetic, non-renally-impaired Friedreich ataxia patient population.

11.5 Reproductive toxicity

Animal studies have demonstrated adverse developmental effects at omaveloxolone exposures below human therapeutic exposure. The compound is classified as a potential teratogen. Pregnancy testing before treatment initiation and effective contraception during treatment and for 28 days after the last dose are required [4].

12. Comparative Assessment

This section presents a structured comparative assessment of five Nrf2-modulating or Friedreich ataxia-relevant compounds against omaveloxolone, evaluated on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The comparators were selected as the principal Nrf2 activators with clinical data or as compounds specifically studied in Friedreich ataxia.

12.1 Dimethyl fumarate (Tecfidera/Vumerity)

Mechanism: Electrophilic Nrf2 activator that modifies KEAP1 Cys151 through succination. Also inhibits NF-kappaB signaling. Approved for relapsing forms of multiple sclerosis (FDA 2013) [34].

Novelty: Low. Dimethyl fumarate and its prodrug diroximel fumarate are established clinical agents with well-characterized Nrf2 activation pharmacology. The mechanism of Nrf2 activation is chemically distinct from the triterpenoid cyanoenone (succination versus Michael addition) but converges on the same KEAP1 cysteine target.

Effect size: In multiple sclerosis, dimethyl fumarate reduces annualized relapse rate by approximately 44 to 53 percent versus placebo and reduces new MRI lesion counts. In Friedreich ataxia, dimethyl fumarate has not produced significant clinical benefit. In a direct preclinical comparison in frataxin-knockout mice with severe cardiomyopathy, omaveloxolone improved cardiac function whereas dimethyl fumarate did not [28].

Promising potential: Low for Friedreich ataxia. Dimethyl fumarate is established for multiple sclerosis but has not demonstrated efficacy in the Friedreich ataxia population. The inferior preclinical performance relative to omaveloxolone in the cardiac Friedreich ataxia model suggests insufficient potency or tissue exposure for this indication.

Side-effect profile: The principal adverse events are gastrointestinal (nausea, diarrhea, abdominal pain, occurring in approximately 30 to 40 percent of patients) and flushing (approximately 30 to 40 percent). Progressive multifocal leukoencephalopathy (PML) has been reported in patients with prolonged severe lym-

phopenia during dimethyl fumarate treatment. The gastrointestinal burden is comparable to omaveloxolone; the PML risk is a distinguishing safety concern absent from the omaveloxolone profile.

Overall validation: High for multiple sclerosis. Low for Friedreich ataxia. The compound is extensively validated as a clinical Nrf2 activator but does not address the specific therapeutic needs of Friedreich ataxia.

Comparison to omaveloxolone: Omaveloxolone is a more potent Nrf2 activator (lower CD value for NQO1 induction), has demonstrated clinical efficacy in Friedreich ataxia, and has shown superior cardiac protection in preclinical Friedreich ataxia models. Dimethyl fumarate has the advantage of a longer clinical track record, broader approved indications, and better-characterized long-term safety (over 10 years of postmarketing data in multiple sclerosis).

12.2 Sulforaphane

Mechanism: Isothiocyanate phytochemical that activates Nrf2 through modification of multiple KEAP1 cysteine residues (including Cys151, Cys273, Cys288). Derived from glucoraphanin in cruciferous vegetables (broccoli, broccoli sprouts) through myrosinase-catalyzed hydrolysis [35].

Novelty: Low. Sulforaphane is the prototypical dietary Nrf2 activator and has been studied for over 30 years. The mechanism is well characterized at the molecular level.

Effect size: Sulforaphane has demonstrated Nrf2 activation and downstream cytoprotective effects in numerous preclinical models. Clinical trials have been conducted in autism spectrum disorder, prostate cancer prevention, chronic obstructive pulmonary disease, and other indications, with modest and inconsistent clinical effects. No clinical data exist in Friedreich ataxia. The compound has not met regulatory endpoints in any indication [35, 36].

Promising potential: Low to moderate as a therapeutic agent; high as a research tool and dietary supplement. The principal limitation is pharmacokinetic: sulforaphane has a short plasma half-life (approximately 1 to 2 hours), low oral bioavailability that varies with formulation and dietary source, and rapid glutathione conjugation and renal elimination [36].

Side-effect profile: Generally well tolerated. Gastrointestinal effects (bloating, flatulence, altered bowel habits) are common at higher doses. No serious adverse events have been reported in clinical trials.

Overall validation: Low as a pharmaceutical agent. Moderate as a research tool. The compound has not met regulatory endpoints despite extensive clinical investigation.

Comparison to omaveloxolone: Omaveloxolone is orders of magnitude more potent as an Nrf2 activator, has a dramatically longer half-life (57 hours versus 1 to 2 hours), and has demonstrated clinical efficacy in a regulatory-grade trial. Sulforaphane has the advantage of a favorable safety profile, wide availability, and low cost, making it a reasonable dietary complement but not a therapeutic substitute for omaveloxolone in Friedreich ataxia.

12.3 Bardoxolone methyl (CDDO-Me, RTA 402)

Mechanism: Semi-synthetic oleanane triterpenoid Nrf2 activator structurally related to omaveloxolone, with a methyl ester at C-28 instead of the difluoropropanamide at C-17. First-generation CDDO-series clinical candidate [16, 17].

Novelty: Low. The compound is the direct structural predecessor of omaveloxolone and shares the same pharmacophore (A-ring cyanoenone) and primary mechanism of action.

Effect size: In the Phase 2 BEAM trial in chronic kidney disease, bardoxolone methyl produced a clinically meaningful improvement in estimated glomerular filtration rate (eGFR) of approximately 5 to 10 mL/min/1.73 m² versus placebo at 52 weeks [16]. The eGFR effect was among the largest observed with any pharmacotherapy in chronic kidney disease, though the mechanism (hemodynamic versus structural renal benefit) remains debated.

Promising potential: Moderate. The Phase 3 BEACON trial in stage 4 CKD with type 2 diabetes was terminated for excess heart failure and cardiovascular mortality [17]. Subsequent Phase 3 trials in different CKD populations (the CARDINAL trial in Alport syndrome, the FALCON trial in autosomal dominant polycystic kidney disease) have reported mixed results. The compound remains in active development for selected nephrology indications in Japan (marketed as Edia by Kyowa Kirin for CKD in rare diseases).

Side-effect profile: The BEACON trial identified clinically significant fluid retention, hypertension, and heart failure as the principal safety concerns. Muscle spasms, weight loss, and gastrointestinal effects were also common. The cardiovascular signal was the basis for trial termination and has fundamentally limited the clinical utility of the compound [17].

Overall validation: Moderate. The compound has demonstrated pharmacological proof-of-concept for Nrf2 activation in kidney disease but carries a serious cardiovascular safety liability that limits clinical application. The BEACON failure directly motivated the structural optimization that produced omaveloxolone.

Comparison to omaveloxolone: Omaveloxolone was specifically designed to address the safety limitations of bardoxolone methyl. The two compounds share the triterpenoid Nrf2 activation mechanism but differ in the C-17/C-28 substituent, which alters tissue distribution, off-target pharmacology, and the cardiovascular safety profile. Omaveloxolone has demonstrated clinical efficacy without the cardiovascular signal that limited bardoxolone methyl, though the patient populations (Friedreich ataxia versus CKD with diabetes) are fundamentally different and direct safety comparisons are limited by this confounding.

12.4 Idebenone

Mechanism: Synthetic short-chain analog of coenzyme Q10 (ubiquinone). Functions as an electron carrier that can bypass impaired complex I in the mitochondrial electron transport chain, shuttling electrons directly to complex III. Also acts as an antioxidant through direct radical scavenging. Does not activate Nrf2 [37].

Novelty: Low. Idebenone has been studied for over 30 years in various mitochondrial and neurodegenerative diseases.

Effect size: In Friedreich ataxia, idebenone has produced inconsistent results across multiple clinical trials. The largest trial, the MICONOS study (Phase 3, 232 patients), failed to meet its primary endpoint of change in the International Cooperative Ataxia Rating Scale (ICARS) at 12 months [37, 38]. Some earlier smaller studies reported cardiac benefits (reduction in left ventricular hypertrophy) at high doses (up to 2250 mg daily), but neurological endpoints have not shown consistent

benefit. The compound is approved for Leber hereditary optic neuropathy (LHON) in the European Union (as Raxone) but is not approved for Friedreich ataxia in any jurisdiction.

Promising potential: Low for Friedreich ataxia. The compound has been extensively studied and has not demonstrated sufficient neurological efficacy to warrant regulatory approval for this indication. Off-label use persists in some clinical settings, particularly for cardiac manifestations.

Side-effect profile: Generally well tolerated. Gastrointestinal effects (nausea, diarrhea) are the most common adverse events. Chromaturia (orange-brown urine discoloration) is common and benign. No serious safety concerns have been identified.

Overall validation: Moderate for LHON. Low for Friedreich ataxia. The compound has extensive clinical experience but has not met registration endpoints in Friedreich ataxia despite multiple large trials.

Comparison to omaveloxolone: Omaveloxolone and idebenone target different aspects of the Friedreich ataxia pathophysiology. Omaveloxolone activates the Nrf2 transcriptional program, which produces a coordinated and sustained upregulation of cellular antioxidant defenses, whereas idebenone provides a direct mitochondrial electron carrier bypass without engaging the transcriptional antioxidant response. Omaveloxolone has demonstrated statistically significant neurological benefit in a registration-quality trial; idebenone has not. The combination has not been formally studied and the clinical utility of adding idebenone to omaveloxolone therapy is unknown.

12.5 EPI-743 (vatiquinone)

Mechanism: Para-benzoquinone that functions as an oxidoreductase cofactor, targeting 15-lipoxygenase (15-LOX) and acting as a potent antioxidant that can regenerate glutathione from its oxidized form. Does not directly activate Nrf2 but modulates the cellular redox state through a complementary mechanism [39].

Novelty: Moderate. The 15-LOX inhibition mechanism is distinct from Nrf2 activation and from the electron carrier function of idebenone, representing a genuinely different pharmacological approach to mitochondrial oxidative stress.

Effect size: In Friedreich ataxia, EPI-743 (vatiquinone) has been evaluated in a Phase 2 trial (the MOVE-FA trial, NCT01962363) in 62 patients over 24 months. Initial reports indicated a trend toward neurological stabilization in treated patients compared to natural history controls, but the Phase 3 registration program (FRAMES trial, NCT04577352) did not meet its primary endpoint. The compound has also been studied in Leigh syndrome and other inherited mitochondrial diseases with variable results [39, 40].

Promising potential: Low to moderate. The Phase 3 result in Friedreich ataxia was negative, limiting the immediate regulatory path. The compound continues in development for other mitochondrial diseases.

Side-effect profile: Generally well tolerated. Diarrhea and gastrointestinal effects are the most commonly reported adverse events. No serious safety concerns have been identified in clinical trials.

Overall validation: Low to moderate. The compound has produced suggestive Phase 2 data in Friedreich ataxia but has not demonstrated Phase 3 efficacy. The clinical development program is less mature than the omaveloxolone MOXIe program.

Comparison to omaveloxolone: Omaveloxolone has the clear advantage of positive Phase 2/3 data and FDA approval, whereas EPI-743 has not met its Phase 3 primary endpoint in Friedreich ataxia. The mechanisms are complementary rather than overlapping (Nrf2 transcriptional activation versus 15-LOX inhibition and glutathione regeneration), and the combination could theoretically address multiple nodes of the oxidative stress cascade in Friedreich ataxia, though this combination has not been studied.

12.6 Comparator summary

The five comparators occupy distinct positions in the Nrf2 activation and Friedreich ataxia therapeutic landscape. **Dimethyl fumarate** is a validated clinical Nrf2 activator for multiple sclerosis but has not demonstrated efficacy in Friedreich ataxia and showed inferior cardiac protection in preclinical Friedreich ataxia models. **Sulforaphane** is a dietary Nrf2 activator with insufficient potency and pharmacokinetic properties for therapeutic application in Friedreich ataxia. **Bardoxolone methyl** is the structural predecessor of omaveloxolone that demonstrated pharmacological proof-of-concept for triterpenoid Nrf2 activation but carries a serious car-

diovascular safety liability. **Idebenone** is a mitochondrial electron carrier with extensive but negative clinical data in Friedreich ataxia neurological endpoints. **EPI-743 (vatiquinone)** is a 15-LOX inhibitor with a complementary mechanism that did not meet Phase 3 endpoints in Friedreich ataxia.

Omaveloxolone occupies a unique position in this landscape as the only compound with demonstrated clinical efficacy in a registration-quality Friedreich ataxia trial, the only compound with FDA and EMA approval for this indication, and the most potent synthetic Nrf2 activator with a manageable safety profile. The aminotransferase elevation signal requires ongoing hepatic monitoring but has not been associated with clinically significant liver injury. The long-term safety and efficacy data through four years of continuous treatment support the position of omaveloxolone as the current standard of care for pharmacotherapy of Friedreich ataxia.

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