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Research Article

A Review On Omaveloxolone

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ABSTRACT

Omaveloxolone is a semisynthetic triterpenoid used to treat friedreich's ataxia. It is the second generation oleananetriterpenoid Nrf2 inducer with antioxidant and anti-inflammatory properties. It is currently used to test in medical trials for freidreich's ataxia, a genetic, multi –organ disease involving mitochondrial dysfunction. It is a nuclear factor erythroid 2 related factor 2 (Nrf2) activator. It is reviewed under Food and Drug Administration and it has the potential to first approved treatment for friedreich's ataxia. Omaveloxolone is not the cure for friedreich's ataxia, it is the first agent targeting to reach NDA submission. It is the rational and potent therapy that is probably disease modifying in the treatment of friedreich's ataxia. Omaveloxolone (RTA-408) is an Nrf2 activator, which decreases the susceptibility of cells through oxidative stress and it leads to cell death and tissue degradation. It is good tolerated not having any significant long term adverse effects. Treatment with RTA-408 remarkably improved in the neurological function, it is measured by modified Freidreich's Ataxia Rating Scale.

DISCOVERY

Omaveloxolone is the drug used to treat friedreich's ataxia. Friedreich's Ataxia is defined as the rare autosomal recessive degenerative disorder. It causes progressive damage to nerves and degeneration of nerve tissue in the spinal cord and also damages the peripheral nerves and cerebellum. It is also characterized by Difficulty in walking, cardiomyopathy, scoliosis, dysarthia, impaired speech and vision loss. It is named after Nikolaus Friedreich the German physician who first described the conditions in 1863. It is also known as friedreich's ataxia, spinocerebular ataxia. It is designed to activate the protein called Nrf2 which helps to regulate the bodies

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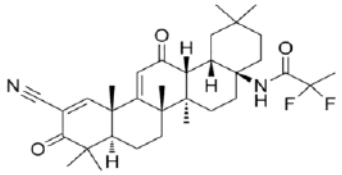
antioxidant response and reduce information. The use of RTA-408 for the treatment of condition involved in mitochondrial dysfunction. Omaveloxolone sold under the brand name Skyclarys. RTA-408 is a second generation orally bioavailable synthetic oleananae triterpenoid. It is produced by reata pharmaceuticals and it is tested in clinical trials for mitochondrial diseases, cancer and to protect against radiotheraphy–induced skin damage and ophthalmic surgery induced corneal damage. The Food and Drug Administration approved the first drug of reata pharmaceuticals as the Skyclarys.

HISTORY:

In 2009, researchers from the laboratory of Dr. Pierre Rustin at Inserm in paris published a paper, that demonstrates the FA cells do not produce enough protein that helps to protect the cells from stress. This protein called Nrf2 is critically important in protecting cells from oxidative stress. This work was supported by freidreich's ataxia patient organization in France, Switzerland and US. In 2013, Dr.Gino Cortopassi's laboratory at the University of California Davis shown that Nrf2 levels were significantly decreasing in tissues of nervous system, the dorsal root ganglia (DRG) and the cerebellum of Freidreich's Ataxia mouse model. Others researchers from different institutions around the world some of them Foreign Agents Registration Act funded have shown the positive effects of Omav. The research has continued with other researchers. In 2015, the company begins to test the Nrf2 activator now called Omav in people with friedreich's ataxia. The phase 2/3 clinical trial showed safety and positive effect from Omav. In 2020, Reata approached the Food and Drug Administration about applying for New Drug Application approval of Omav to treat friedreich's ataxia. The Food and Drug Administration was not convinced that single clinical trial that provided enough evidence of effectiveness of Omav. In 2021, Foreign Agents Registration Act again launched into action coordinating the petition signed by 74,070 individual, requesting the Reata pharmaceuticals submit a New Drug Application. Food and Drug Administration consider a approval of New Drug Application for omav in friedreich' s ataxia based on existing evidence from clinical trials. Reata analysed and shared data from open label extension study Food and Drug Administration and after reviewing this new data. Reata is continued to collect and share more data on long term effect of Omav. In 2023, the Food and Drug Administration decides to approve the application, this would be the first approval treatment for friedreich's ataxia in US.



(Figure. 1) Structure of Omaveloxolone

PHYSICOCHEMICAL PROPERTIES:

(Table 1): Physicochemical Properties of Omaveloxolone

Chemical Name	Propanamide, N — (2- cyano- 3,12 dioxo -28- noroleana1,9 (11)-dien-17-yl)-2-2-difluro
Class	Miscellaneous central nervous system
Molecular fonnula	C33H44F2N203
Molecularweight	554.71
Boilingpoint	662^{O} C±55^{o}C
Solubility profile	Soluble in DMSO upto 20 mg per ml , insoluble in water
Description	Powder

Colour	Green/ Blue
Quality Assurance	> 98% purity assayed by High Performance Liquid Chromatography and Nuclear Magnetic Resonance
Blood Brain Barrier	Penetrant
Storage	Store Skyclmysat room temperature between 68^0F to 77^0F
Ultraviolet (W)	7" max 239nm

PHARMACOKINETIC PROPERTIES:

Absorption:

The average time to achieve peak plasma concentration is 7to 14 hours. Omaveloxolone has the total plasma that revelation is based on area under the concentration – time curve (AUC). This increasing the dose – dependent and dose proportional manner over the dose range is 50 mg to 150 mg, but the maximum plasma concentration (Cmax) of RTA-408 increased in a less than dose proportional manner over the dose range in healthy fasted subjects.

Distribution:

Skyclarys has the mean apparent volume of distribution is 7361L (105 L/kg for 70 kg person). Protein Binding of Skyclarys is 97%.

Metabolism:

The metabolism of RTA-408 is predominantly by CYP3A, with slight metabolism by CYP2C8 and CYP2.

Excretion:

Consequent administration of the single oral dose of radiolabelled RTA-408 150 mg to healthy subjects, almost 92% of the dose were recovered in feces (almost 91% within 96 hours after administration) and 0.1% in urine.

(Table 2): Pharmacokinetic Properties of Omaveloxolone

Tmax	10hr
Cmax	44.8±49.7
$t_{1/2}$	57hr
BCS Class	BCS Class II drug
Clearance	109L/h
PKa	7.26

PHARMACODYNAMICS:

Omaveloxolone is commonly affecting many pharmacodynamic markers they are Ferritin and GG, it is demonstrated invitro and then in other human studies. As the sihn of robust Nrf2 activation, Plasma Ferritin and GGT, ALT and AST enlarged significantly after four weeks of treatment with Skyclarys. An increase in selected Nrf2 target gene expression were noticed during the time of treatment, it acrossing the dose levels. The interpretation is restricted by higher than expected variation between samples in assay. Likewise, the dose dependent expands in mRNA expression of select Nrf2 antioxidant genes is follow across dose levels.

One patient treated with Skyclarys 40 mg and the three participants treated with Skyclarys 160 mg has been increased in trans aminases greater than 3 times the upper limit of normal, but these concurrently dropped to normal while taking RTA-408 treatment. The changes of transaminases are not related with signs or symptoms of liver injury and simultaneously bilirubin level increased is not observed.

MECHANISM OF WORKING:

Skyclarys acts as the activator of nuclear factor erythroid2 –related factor 2 (Nrf2) pathways that lead to increased production of antioxidant and anti –inflammatory molecules, which helps to diminish oxidative stress, inflammation and cell damage. It works by binding to the protein called Keap 1, this keeps Nrf2 in the inactive state. By binding to Keap1, Skyclarys put a stop to the

degradation of Nrf2 and allows it to accumulate in the cell.

Once inside the cell, Nrf2 translocate to the nucleus and binds to specific DNA sequences known as antioxidant response elements (AREs) in the promoter regions of target genes. In normal conditions, Nrf2 level were regulated by kelch – like ECH – associated protein 1 (KEAP1) which binds and avoid Nrf2 translocation to the nucleus. In patients with friedreich's ataxia, the Nrf2 signalling pathway is dysfunctional and Nrf2 as the lower activity due to its continuous proteasomal degradation.

The Nrf2 were activated by Skyclarys that describes the therapeutic effect. Omaveloxolone has other activity that is the inhibition of NF – kB signalling pathway, promoting the mechanism such as anti-apoptotic, antioxidative and anti-inflammatory.

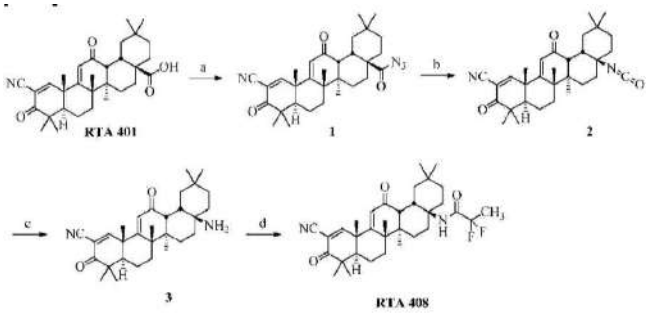
For the patient with Friedreich's Ataxia, the drug omaveloxolone is given, it shown the activity of potential therapeutic effect that is the activation of Nrf2. Omaveloxolone through Nrf2, It activates intracellular and mitochondrial antioxidative pathways, in further more pathways that might directly increase the mitochondrial biogenesis. Nrf2 regulates multiple genes that anti oxidative potential and the production of cellular energy within the mitochondria by both direct and indirect roles.

METHODS OF SYNTHESIS:

RTA-408 can be prepared according to the method illustrated below. These methods can be further modified and optimized using the principle and techniques of organic chemistry. It should be accepted that the particular anion or cation forming the part of any salt of that invention is not captious, so long as the salt, as whole is pharmacologically acceptable. Further example for pharmaceutically acceptable salts and their methods of preparation and use were presented in hand book of pharmaceutical salts.

Then, atoms making RTA-408 of present invention are intended to include all isotopic forms of such atoms. Isotopes is used herein, including those atoms have same atomic number different mass number. By saying in general example and not having any limitation, isotopes of hydrogen cover tritium and deutrium. Then it is consider that one or more carbon atom of compound in the present invention perhaps replaced by a silicon atom.

RTA-408 and polymeric form also have the advantage that they have more efficacious than, less toxic than ,longer acting than ,more potent than, producing lesser side effects than, more easily absorbed than, have the better pharmacokinetic profile than and have other pharmacological, chemical, or physical advantages over the compounds known in the prior art for use in indication stated here.



(Figure. 2) Synthesis of Omaveloxolone

a- DPPA, trietylamine, toluene, 0 to room temperature.

b- Benzene, 80 for 2 hours.

c- HCL, CH3CN, CH3CF2CO2H, DCC, DCM.

d- 12N HCL, MeCN 0 to room temperature.

MEDICINAL USES:

Epilepsy: Potential benefit (preclinical)

In a kainic acid mouse model of epilepsy, Omaveloxolone treatment following the seizure induction restored glutathione and ATP levels and decreased neuronal loss in the hippocampus. The mechanism of protection from excitotoxicity may require protecting neuronal mitochondria. Pre-

treatment of cortical neurons with Omaveloxolone protecting mitochondrial depolarization and neuronal death during epileptiform activity. This intimates that Omaveloxolone can prevent neuronal mitochondria from excitotoxic stress, however it remains to be determined if this protection elongate to other types of neuronal stressors.

Anesthesia-related cognitive impairment: Potential benefit (Preclinical)

Omaveloxolone protected against propofol-induced cognitive disablement in neonatal mice based on performance on the Morris water maze. It relieve the propofol-mediated activation of NF-kB, pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β), and caspase-3-induced neuronal cell death through the activation of Nrf2. This recommend that Omaveloxolone might help protect against acute inflammation and oxidative-stress-mediated cognitive impairment, however it is indefinite whether it would offer same benefit to older animals with having less robust endogenous antioxidant-induction capacity and/or in the context of chronic disease.

Neuroinflammation: Beside with the preservation/restoration of mitochondrial function, the mitigation of inflammation is expected it has been one of the primary neuroprotective mechanisms of Omaveloxolone. Activation of Nrf2 can prohibit the pro-inflammatory NF-kB signaling pathway. In cultured rat astrocytes, treated with Omaveloxolone elongated reactive oxygen species (ROS) production, NF-kB activation, and matrix metalloprotease-9 (MMP-9) induction in response to IL-1ß. It has not been unaltered which cell types are the primary targets of Omaveloxolone in vivo.

Aging and related health concerns:

It expands opposition of mitochondria to oxidative stress damage in mitochondrial diseases, but it is unreasonable whether it can also protect mitochondria in the context of aging.

Mitochondria-associated diseases:

The results of two Phase 2 RCTs, while preliminary and insufficiently powered, provide assist for the possible beneficial effect of Omaveloxolone on mitochondrial function in humans. Though, it is not yet known whether Omaveloxolone can develop the mitochondrial function in the absence of pathology or protect against age-related mitochondrial dysfunction.

Mitochondrial myopathy:

Omaveloxolone leads to Nrf2 activation in patients based on the pharmacodynamic measure of increased ferritin levels. Based on the reports of this study Reata Pharmaceutical does not appear to be continuing clinical development of Omaveloxolone for this indication, at this time.

Friedreich's ataxia:

Friederichs's ataxia is the progressive neurodegenerative disease of the spinal cord that affects motor function. It is caused by a mutation in the mitochondrial protein called frataxin, it leads to mitochondrial complex I inhibition. Mitochondria in these patients are particularly endangered to oxidative stress. In vitro studies using patient derived cells tells that Omaveloxolone can enlarge the objection of mitochondria to oxidative stress.

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. 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 was improvements in each of the

four subsections, with the highest effect were seen in upright stability. Pediatric patients showed the greatest benefit. There was nominal statistical importance on the secondary endpoint of Friedreich's ataxia-activities of daily living 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 and the clinical global impression of change, 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 reports from this study, Reata Pharmaceuticals has received Fast Track Designation from the Food and drug administration for the development of Omaveloxolone for Friedreich's ataxia. They plan to file a New Drug Application in the first quarter of 2022.

Radiation damage: (Preclinical)

Triterpenoids has shown to provide prevention of healthy cells from radiation damage in rodent models. In mice getting a lethal dose (0% survival after 30 days) of radiation Omaveloxolone pre-treatment prevented lethality (100% survival after 30 days) by conserving the integrity of intestinal lining.Additionally, when used in combination with radiotherapy in prostate cancer tumor xenograft model, Omaveloxolone increased the inhibition of tumor growth comparing to radiation alone.The drug Omaveloxolone is also prevented against chronic radiation (40 Gy) toxicity in rats. It protected tissue necrosis, undefiled the vascular integrity, and then activated adipogenesis/angiogenesis gene transcriptional plan of action in the skin. Omaveloxolone were also shown to inspire wound curing in rodent models of chronic venous deficiency and diabetes. 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 good safety in healthy volunteers, but reports of the Phase 2 testing its capability to protect against radiation activated dermatitis in breast cancer patients has not been made available, inspite of concluding in 2015. If shown to be effective in humans, this type of lotion could effectively also be helpful to protect against damage from day by day sources of environmental radiation.

Neuropathy: Potential benfit (Preclinical)

In mouse model of neuropathic pain, chronic constriction injury of the sciatic nerve, intrathecal Omaveloxolone treatment backward mechanical allodynia and thermal hyperalgesia in dose-dependent manner . The analgesic effect was dependent on the Nrf2-mediated induction of PGC-1α, the systematic of mitochondrial biogenesis. However, Omaveloxolone stoped to show neuroprotective activity in the rat model of ischemic optic neuropathy.

Osteoporosis: Potential benfit (Preclinical)

Bone reabsorbing osteoclast differentiation is begined by receptor activator of nuclear factor-κB ligand , and this process leads to the manufacture of Reactive oxygen species. Omaveloxolone is setup to inhibit rankl-mediated osteoclastogenesis. The inhibition of rankl were associated to the capability of Nrf2 to diminsh sting. Treatment with omaveloxolone is found to hinder osteoclast differentiation and then bone resorption in cell culture and to devaluate bone loss in the mouse model of ovariectomy-induced bone loss by decreasing the production of osteoclasts.

Nonalcoholic steatohepatitis: Potential benfit (Preclinical)

Treatment also improved by blood glucose control based on the deductions in non-fasting blood glucose and glycated hemoglobin A1C concentrations. Interval, there were reductions in liver and serum triglycerides, there were elevations in serum total, high density lipoprotein, and low density lipoprotein cholesterol. The effect on cholesterol were 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 designated of Nrf2 target genes, includes ferritin heavy chain.

ADVERSE EFFECTS:

Muscular Skeletal Pain (20%), Aspartate AminoTransferase /Alanine Amino Transferase (AST /ALT), Oropharyngeal pain, Muscle spasm, Back Pain, Rash,Decreased Appetite, Abdominal Pain, Bone or joint pain, Mouth or Throat Pain, Flu like Symptoms, Higher liver damage, Moderate and severe hepatic impairment, Yellowing Eyes/Skin, Dark Urine, Pounding Heart Beat, Shortness of breath, Swelling ankles/ feets /hands, Sudden/Unexplained weight gain, Lipid Abnormalities, Elevation of B-type natriuretic peptide (BNP).

TREATMENT OF OVERDOSE:

There are no about the overdose of omaveloxolone. Overdose is likely to increase the serious of adverse effects it includes the levels of cholestral, B-type natriuretic peptide (BNP), Elevation of liver enzymes AST and ALT.

INTERACTION:

Drug interaction:

1. Moderate or strong CYP3A4 inhibitors use with Skyclarys reduces the dosage with monitoring if use is unavoidable.
2. Avoid simultaneous use of Skyclarys with Moderate or Strong CYP3A4 Inducers.
3. Counsell the females to use the alternative contraceptive method (e.g. Non-hormonal intra uterine system) or additional –non hormonal contraceptive (e.g. condoms) during simultaneous use and for 28 days after the termination of Skyclarys.
4. The Phase 1 clinical trial (NCT04008186) were conducted testing the potential interactions between RTA- 408 and the variety of substrates and drug transporters, inducer of metabolic enzymes.
5. It includes the Digoxin tablets, Midazolam oral solution, Gemfibrozil tablets, Metformin 500mg oral tablet and Verapamil pills. No matter how, the results had not been posted and potential drug interaction had not been disclosed.
6. Omaveloxolone's serum concentration is increased when combined with Abametapir.
7. The metabolism of Alectinib is increased when combined with Omaveloxolone.
8. When combined with Omaveloxolone , the serum concentration of Albendazole is reduced.
9. Serum Concentration of 1, 2-Benzodiazepene is diminished when the drug omaveloxolone is combined .
10. When Omaveloxolone is combined with Abemaciclib its serum concentration is reduced.
11. Abiraterone serum concentration is decreased when it is combined with Omaveloxolone.
12. Reduction of serum concentration of Acalabrutinib it happens when it is combined with Omaveloxolone.
13. Adagrasib serum concentration is reduced due to combination of Oamveloxolone.
14. Acenocoumarol serum concentration is decresed combined with Omaveloxolone.

15. Acetaminophen is combined with Omaveloxolone its serum concentration is decreased.

Food Interaction:

Omaveloxolone capsules has been taken in anycase one hour before eating on empty stomach. The high fat meal enlarged the Cmax and AUC by approximately 350% and 15% when compared to the fasting conditions.

Warnings:

1. Elevation liver enzymes Alanine transaminase and Aspartate Transaminase in the blood caused by Omaveloxolone. Use with caution in the patients with pre existing disablement of liver function. Before initiating Omaveloxolone, check the patient Alanine transaminase, Aspartate Transaminase and Bilirubin levels, and then monitor every months for the first three months of treatment.
2. If Alanine transaminase and Aspartate Transaminase were higher than five times upper limit of normal (ULN) or higher than three times Upper Limit Normal additionally high Bilirubin level, stop Omaveloxolone monitor liver function.
3. Omaveloxolone cause an increased in the levels of Brain-Type Natriuretic Peptide. Elevation of Brain- Type Natriuretic Peptide that intimate heart failure. If the patients developing the symptoms of fluid overload and cardiac function and then evaluate the Brain-Type Natriuretic Peptide and stop Omaveloxolone if mandatory.
4. The effectiveness of Hormonal contraceptive is decreased by the drug Omaveloxolone.
5. Increase in low density lipoprotein cholesterol and decreased in high density lipoprotein cholesterol level these both are accomplished by Omaveloxolone . Monitor patients cholesterol level then it is controlled appropriately.

Use in specific population:

Females and Males of Reproductive Potential:

Skyclarys might decline the potency of hormonal contraceptives. Avoid subsequent use with combined hormonal contraceptives (eg: Pills, Patch), Implants and progestin only pills, these advice were given to patients.

Lactation:

In human milk there is no data for Omaveloxolone or its metabolites. The effects on milk production and breast feed infants were unrevealed. In oral administration Omaveloxolone is excreted in milk of lactating rat. The Health benefits and Development of Breast feeding shall be intended along with the mother's clinical need for Skyclarys and potential of any adverse effects on the breast feed infant from the Skyclarys.

Geriatric Use:

In Friedreich's Ataxia the clinical studies of Skyclarys did not cover patients aged 65 and over.There are no data provided for determine whether the patients respond differently than younger adult patients.

Pediatric Use:

For the treatment of Friedreich's Ataxia the safety and effectiveness of Skyclarys has been established in pediatric patients aged 16 years and older. Using Skyclarys for this treatment was helped by evidence from one adequate and well controlled studies.

Hepatic impairment:

Plasma exposure of Omaveloxolone is expanded in patients with moderate or severe hepatic impairment. With the patient having severe hepatic impairment avoids use of skyclarys.

Pregnancy:

There are no sufficient data on the development risks associated with the use of Skyclarys in pregnancy time. In the US generally pregnancy recognised is 2% to 4% and 15% to 20% respectively. The background risk of major child

birth defects and Miscarriage for the population is unknown.

CONVENTIONAL MARKETED FORMULATION:

(Table 3): Conventional Marketed Formulation of Omaveloxolone

Types	Capsules
Brand name	Skyclarys
Company name	Reata Pharmaceuticals
Dose	50 mg
Prize	USD 450

NOVEL MARKETED FORMULATION:

(Table 4): Novel Marketed Formulation of Omaveloxolone

Types	Capsules
Brand name	Skyclarys
Company name	Reata Pharmaceuticals
Dose	50 mg
Prize	USD 450

Toxicity:

Toxicity information related to Skyclarys is not readily available. In the bacterial reverse mutation (Ames) assay, the negative reports were appeared by Omaveloxolone, the chromosomal aberration assay in human peripheral blood lymphocytes were shown the positive reports. Rats given 0, 1, 3 and 10 mg /kg/day of taking oral administration of skyclarys having the higher incidence of pre – and post- implantation loss and resorbtions that leads to diminish in viable embroys at the largest dose. Increased risk of severe adverse effects includes elevation in hepatic transaminases and B-type Natriuretic peptide (BNP), and lipid abnormalities, these causes by overdose of Omaveloxolone in patients. Carcinogenicity of Skyclarys has not been determined. There are no effect dose (3mg/kg/day) of skyclarys for reproductive functions adverse effects and fertility, they were identical to AUC of almost two times recommended human dose (150) mg per day.

CONCLUSION:

Omaveloxolone 50 mg is well tolerated, didn't lead to change in the primary outcomes measures, but there is improvement in the investigational end points that is reducing heart rate and during submaximal exercise, there is production of milk, persistant with having improvement in mitochondrial function and submaximal exercise patience. This indicates the determined benefit if Omaveloxolone treatment on diseases of friedreich ataxia. Omaveloxolone as the potential benefit in patients with mitochondrial myopathy which motivate more investigations of omaveloxolone in patient group. Our finding tells that drug is tolerated a patients with having advanced solid tumours. At dorsals which is the activation of Nrf2 pathway, which having priority review under orphan drug status and rare peadritic disease designation.

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