Report Omaveloxolone –SKYCLARYS®

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance:omaveloxolone **Brand Name:**Skyclarys® **Originator/licensee:**Reata Ireland Limited **Classification:**NCE **ATC code:**not yet assigned **Orphan Status:** **Eu:** Yes **Us:** Yes **Mechanism of action:** omaveloxolone activates the Nrf2 pathway which is involved in the cellular response to oxidative stress. The precise mechanism by which omaveloxolone exerts its therapeutic effect in patients with Friedreich's ataxia is unknown, but as Nrf2 activity is reduced in patients with Friedreich's ataxia, Nrf2 activators may be involved [1].	**Authorized Indication:** **EMA:**omaveloxoloneis indicated for the treatment of FA in adults and adolescents aged ≥16 years [1]. **FDA:** omaveloxoloneis indicated for the treatment of FA inadults and adolescents aged 16≥years [2]. **Route of administration:**os **Licensing status** **EU CHMP P.O. date:**14/12/2023 **FDA M.A. date:**28/02/2023 **EU Speed Approval Pathway:**No **FDA Speed Approval Pathway:**Yes ----- **ABBREVIATIONS:** **AE**: adverse event **ALT**: alanine aminotransferase **ARP**: all randomized pts **AST**: aspartate aminotransferase **CI**: confidence interval **Df**: degrees of freedom **FA**: Friedreich's Ataxia **FAS**: full analysis set **mFARS**: modified Friedreich's Ataxia Rating Scale **Nrf2**: Nuclear factor (erythroid-derived 2)-like 2 ***P***: p-value **Pbo:** placebo **Pes cavus**: multiplanar foot deformity characterised by an abnormally high medial longitudinal arch **Pts**: patients **SAE**: serious adverse event **URTI**: upper respiratory tract infection	**Summary of clinical EFFICACY:** The part 2 of the MOXIe (NCT02255435) study was an international, double-blind, randomized, pbo-controlled, parallel-group, phase II trial to assess the efficacy and safety of omaveloxolone in pts with FA. Eligible pts were 16 to 40 years with genetically confirmed FA and baseline mFARS[1] scores between 20 and 80[2], that could complete maximal exercise testing on a recumbent stationary bicycle. 155pts were screened, and 103 were randomly assigned to receive omaveloxolone (n = 51) or placebo (n = 52), with 40 omaveloxolone patients and 42 placebo patients analyzed in the full analysis set (FAS).FAS was used for primary analysis of efficacy and limited to pts without *pes cavus*, who had at least one postbaseline measurement. The primary outcome was change from baseline in mFARS score in those treated with omaveloxolone compared with those on pbo after 48 weeks. A Changes from baseline in mFARS scores in omaveloxolone (-1.55 ± 0.69; 95% CI = -2.93 to -0.18) and pbo (0.85 ± 0.64; 95% CI = -0.43 to 2.13) pts showed a difference between treatment groups of 2.40 ± 0.96 points (*p* = 0.014; 95% CI = -4.31 to -0.5) [3]. [1]represent individuals just after the time of presentation at the mildest and several years loss of ambulation at the most severe [2]scores range from 0 to 99, with lower scores indicating better neurological function. [3]randomization was stratified by pes cavus (with and without pes cavus) **Summary of clinical SAFETY:** Safety analyses included ARP. The rates of AE were similar in the omaveloxolone group and pbo (both 100%). Most AE were mild to moderate in intensity. **Table 1: Summary of clinical safety** | | Pbo (N=52), n (%) | Omaveloxolone (N=51), n (%) | |---|---|---| | Any AE | 52 (100%) | 51 (100%) | | Any SAE | 3 (6%) | 5 (10%) | | Discontinuation due to AE | 2 (4%) | 4 (8%) | AE occurring in > 20% of pts were: contusion, headache, upper respiratory tract infection, excoriation in both groups, and nausea, ALT increased, fatigue, diarrhea, abdominal pain and AST increased in omaveloxolone group. Apart from increases in aminotransferases, the excess occurrence of AE in pts receiving omaveloxolone was limited to the first 12 weeks of treatment as pts adjusted to treatment and developed improved drug tolerability. SAEs that occurring in up to 2% of pts were: atrial fibrillation, anemia, ankle fracture, craniocerebral injury, gallbladder disorder, laryngitis, noncardiac chest pain, palpitations, sinus tachycardia, vetricularVtachycardia, viral URTI [3]. **Ongoing studies:** ● ***For the same indication:***Yes ● ***For other indications:***Yes **Discontinued studies (for the same indication):**No **References:** [1]. https://www.ema.europa.eu/en/medicines/human/EPAR/skyclarys [2]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216718Orig1s000lbl.pdf [3]. Lynch DR et al. Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study). Ann Neurol. 2021 Feb;89(2):212-225. doi: 10.1002/ana.25934. Epub 2020 Nov 5. Erratum in: Ann Neurol. 2023 Dec;94(6):1190. PMID: 33068037; PMCID: PMC7894504. [4].https://www.drugs.com/price-guide/skyclarys [5]. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=IT&Expert=95 [6]. https://adisinsight.springer.com/search	**Cost of therapy:** The cost for Skyclarys® oral capsule 50 mg is around $32,477 for a supply of 90 capsules [4]. **Epidemiology:** The prevalence in the Caucasian population is estimated at 1/20,000 – 1/50,000 [5]. ----- **POSSIBLE PLACE IN THERAPY** There is no cure for the FA [5]. **OTHER INDICATIONS IN DEVELOPMENT** Mitochondrial disorders; Ocular inflammation; Ocular pain [6]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT**: No **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Nomlabofusp [6]. *Service reorganization: Yes *Possible off label use:

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