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Newcastle University

Health Technology Briefing
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Leriglitazone for treating X-linked adrenoleukodystrophy

Company/Developer	Minoryx Therapeutics Sl

☒ New Active Substance ☐ Significant Licence Extension (SLE)

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Licensing and Market Availability Plans

Leriglitazone is currently in phase II/III clinical trials.

Summary

Leriglitazone is currently being developed to treat male patients with X-linked adrenoleukodystrophy (X-ALD). Adrenoleukodystrophy (ALD) is a degenerative condition where there is a build-up of substances known as "very long chain fatty acids" in tissues around the body, particularly in the brain, spinal cord and adrenal glands. There are three types of ALD: a cerebral form (cALD), adrenomyeloneuropathy (AMN) and Addison's disease only. Symptoms of adrenomyeloneuropathy include sphincter problems, impotence and progressive weakness. People with cALD normally develop symptoms including behavioural problems, loss of fine motor skills and other neurological symptoms. Complete dependence or death can occur from 6 to 24 months from when symptoms started.

Leriglitazone is a medication designed to activate receptors in the body called "PPAR gamma." which control multiple pathways including energy generation and inflammation. Additionally, leriglitazone can potentially improve myelination (the formation of a sheath called myelin around a nerve fibre to enhance conduction) and reduce adhesion of a type of immune cell to the lining of cells in the blood brain barrier, which plays a role in the development of X-ALD. Currently, there are very few treatment options available for patients who have X-ALD. If leriglitazone is licensed, it may provide a novel treatment option for patients with the condition.

Proposed Indication

Treatment of X-linked adrenoleukodystrophy.[1,2]

Technology

Description

Leriglitazone (MIN-102) is a novel, orally bioavailable and selective peroxisome proliferator-activated receptor (PPAR) gamma agonist.[3] In X-linked adrenoleukodystrophy, there is an accumulation of very long-chain fatty acids (VLCFA) in several tissues, including in the brain, peripheral nerves and adrenal glands. Mitochondrial dysfunction, oxidative stress and bioenergetics failure are all linked to the pathogenesis of X-ALD.[4] By activating PPAR gamma, leriglitazone modulates the expression of genes involved in mitochondrial biogenesis, restoring lost energy balance, decreasing oxidative stress and restoring mitochondrial function caused by VLCFA accumulation.[3] Leriglitazone also increases expression of genes involved in oligodendrocytes differentiation.[3] This promotes remyelination and modulates neutrophin levels, improving neuronal survival.[3] In X-ALD, leriglitazone also decreased NF-kB levels, thereby reducing macrophage and microglial activation and, subsequently, neuroinflammation.[3] Leriglitazone has previously been demonstrated to reduce neuroinflammation and improve mitochondrial function in both rodent- and patient-derived cells, with motor symptoms improving in mice with X-ALD.[4]

Leriglitazone is currently being evaluated in male patient with X-ALD in two clinical trials. In a phase II/III trial, male patients aged between 18 to 65 years with adrenomyeloneuropathy phenotype of X-ALD were randomised to receive either leriglitazone orally or placebo (ADVANCE; NCT03231878).[2] A single-arm phase II trial focuses on male children with X-linked cerebral ALD (cALD) prior to haematopoietic stem cell transplantation (HSCT) (NEXUS, NCT04528706).[1] In this trial, leriglitazone is administered as an oral suspension once per day.[1]

Key Innovation

There are currently very few treatment options available to male patients with X-ALD. Adrenal insufficiency can be managed with steroidal replacement therapy and bone marrow transplantation may be considered for male children in the early stages of the disease.[5] International recommendations suggest that treatment of those aged 18 years or older with myeloneuropathy should be aimed at reducing pain (for example with medications such as pregabalin or gabapentin) and spasticity (with spasmolytics e.g. baclofen).[6] The same international recommendations also suggest the use of HSCT or gene therapy to treat cALD.[6]

Leriglitazone at an oral suspension starting dose of 150 mg has already been well-tolerated in adult men with X-ALD in a randomised, double-blind, placebo-controlled phase II-III trial.[7] If licensed, the availability of leriglitazone may provide a novel treatment option for X-ALD.

Regulatory & Development Status

Leriglitazone does not currently have marketing authorisation in the EU/UK for any indication.

Leriglitazone received an orphan designation status in the EU for the treatment of ALD on 18 November 2016.[8] Leriglitazone received FDA fast track designation for all forms for X-linked ALD in 2020.[9]

Leriglitazone is currently in phase II trials for Friedreich's ataxia.[10]

Patient Group

Disease Area and Clinical Need

X-ALD is a recessive disorder caused by disruption to the transportation and breakdown of fatty acids in the peroxisomes (small organelles involved in metabolic reactions) and variants in the ABCD1 gene.[5] As an X-linked disorder, mothers may carry the genes linked to the disease but unless there are other affected children within a family there can be no way to identify who carries the genes.[11] About 20% of carrier females develop milder neurologic symptoms of the condition, which often do not develop until their 40s.[5] X-ALD presents with three main phenotypes: adrenomyeloneuropathy (AMN), cALD and an Addison's disease form only.[5] Symptoms of AMN usually appear in men from their mid-20s.[5] Symptoms of AMN can include progressive paraparesis, sphincter problems, impotence and adrenal insufficiency.[5] Although these symptoms may progress slowly over a number of decades, rapid progression to cALD can occur in between 20% and 60% of men affected with AMN depending on follow-up time.[12-14] cALD occurs in 31-35% of ALD patients in childhood.[12] Children with cALD usually develop symptoms between 4 and 10 years old and affected children can show signs of dementia, behavioural problems, loss of fine motor skills, visual loss or other unexplained neurological symptoms.[5] Progression is variable but can be rapid, leading to complete dependence and death within 6 to 24 months of symptom onset.[5]

ALD is a common peroxisomal disorder estimated to affect around 1 in every 20,000 males worldwide.[5,11] The 2021-2022 Hospital Episode Statistics for England recorded a total of 276 finished consultant episodes (FCE) for disorders of fatty-acid metabolism (ICD-10 code: E71.3), resulting in 238 hospital admissions and 892 FCE bed days and 85 day cases. In total, 201 FCEs were in males.[15]

Recommended Treatment Options

There are currently no guidelines covering the treatment of X-ALD in males from the National Institute for Health and Care Excellence (NICE). However, Health Education England's Genomics Education Programme recommends steroid replacement therapy for patients with adrenal insufficiency.[5] Additionally, bone marrow transplantation can be considered for male children in the early stages of the disease.[5] International guidelines suggest treating those aged 18 years or older with myeloneuropathy with medications aimed at reducing pain (e.g. pregabalin or gabapentin) and spasticity (spasmolytics such as baclofen).[6] For paediatric patients with cALD, these international guidelines recommend treatment with HSCT or gene therapy.[6]

Clinical Trial Information

Trial	**ADVANCE, NCT03231878, EudraCT- 2017-000748-16;** A Randomized, Double-blind, Placebo-controlled, Multinational, Multicenter Study With Open-label Treatment Extension to Assess the Effect of MIN-102 (IMP) on the Progression of Adrenomyeloneuropathy in Male Patients With X-linked Adrenoleukodystrophy **Phase II/III** – Active, not recruiting **Location(s):** Six EU countries, UK and USA **Primary completion date:** June 2021
Trial Design	Randomised, parallel-assignment, placebo-controlled, triple-blinded
Population	N = 116;[7] male patients aged between 18 and 65 years diagnosed with X-ALD based on elevated VLCFA and genetic testing with clinical evidence of spinal cord involvement.
Intervention(s)	Leriglitazone (MIN-102). Oral suspension

Comparator(s)	Placebo
Outcome(s)	Evaluation of the efficacy of leriglitazone on the progression of AMN in male patients using a motor function test (Six-Minute Walk Test; 6MWT) [Time frame: in 96 weeks] See trial record for full list of other outcomes.
Results (efficacy)	There was no between-group difference in 6MWT between those taking leriglitazone (change from baseline -27.7 meters (m), standard deviation (SD) 41.4) and those taking placebo (change from baseline -30.3 m, SD 60.5). The least squares mean difference between groups was 1.2 m (95% confidence interval -22.6 to 20.2, P = 0.91). Post-hoc subgroup analyses suggested that there was a potential between-group difference favouring leriglitazone in patients with early-stage disease for EDSS ambulation.[7] In a post-hoc analysis, radiological progression of cerebral lesions occurred in a smaller proportion of patients receiving leriglitazone group than in the placebo group.[7]
Results (safety)	There were no deaths reported. Serious treatment-emergent adverse events occurred in 14 of 77 (18%) of patients taking leriglitazone and 10 of 39 (26%) of patients receiving a placebo. The most common serious treatment-emergent adverse event was clinically progressive adrenoleukodystrophy, which occurred in 6 of 116 (5%) of patients, all of which were in the placebo group. The most common treatment-emergent adverse events in both the leriglitazone and placebo groups were weight gain and peripheral oedema.[7]

Clinical Trial Information	
Trial	**NEXUS, NCT04528706, EudraCT-2019-000654-59;** An Open-label, Multicenter Study in Male Pediatric Patients With Cerebral X-linked Adrenoleukodystrophy (cALD) to Assess the Effects of MIN-102 Treatment on Disease Progression Prior to Human Stem Cell Transplant (HSCT) **Phase II** – Recruiting **Location(s):** Three EU countries and Argentina **Primary completion date:** December 2023
Trial Design	Single group assignment, open-label
Population	N = 13 (estimated); males aged ≥ 2 and ≤ 12 with diagnosis of X-linked ALD
Intervention(s)	Leriglitazone (MIN-102) taken once daily at a volume specified by the pharmacokinetic specialist to achieve desired plasma exposure. Oral suspension leriglitazone hydrochloride.
Comparator(s)	None.
Outcome(s)	Primary outcomes: 1. Evaluate whether leriglitazone can halt disease progression of cALD if administered prior to hematopoietic stem-cell transplantation (HSCT), as determined by serial clinical and MRI investigations in paediatric subjects. [Time Frame: 6 months to 2 years]

	2. "Arrested disease" defined using change in NFS from baseline, free of MFD and lack of lesion progression on MRI [Time Frame: at 24 weeks and 96 weeks]
Results (efficacy)	Of the 11 patients evaluated at week 24, all demonstrated lesion growth deceleration and remained clinically stable (free of major functional disability and stable neurological function score). Five patients had arrested disease (45.5%, 95% confidence interval 13.9-68.4%) and median (range) change from baseline was 0.0 (0.0-1.0) for neurological function score and 0.0 (0.0-3.0) for Loes score. In most patients, neurofilament light chain concentrations stabilised and matrix metalloproteinase-9 concentrations decreased in all patients.[16]
Results (safety)	Of the 11 patients evaluated at week 24, there were no severe adverse events, treatment-related serious adverse events or deaths.[16]

Estimated Cost

The cost of leriglitazone is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Leriglitazone for treating adrenoleukodystrophy (GID-HST10049). TBC.

NHS England (Policy/Commissioning) Guidance

- NHS England. 201/14 NHS Standard Contract For Metabolic Disorders (Adult). E06/S/a.
- NHS England. 2013/14 NHS Standard Contract For Metabolic Disorders (Children). E06/S/b.
- NHS England. 2013/14 NHS Standard Contract For Metabolic Disorders (Laboratory Services). E06/S/c.
- NHS England. Service specification: Inherited White Matter Disorders Diagnostic and Management Service (IWMD) (All Ages).

Other Guidance

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Additional Information

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