NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JULY 2020

Levosimendan for respiratory function in amyotrophic lateral sclerosis

NIHRIO ID	11458	**NICE ID**	10088
Developer/Company	Orion Pharma (UK) Ltd	**UKPS ID**	649505

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Levosimendan is in clinical development for the treatment of respiratory function in amyotrophic lateral sclerosis (ALS). ALS is a progressive disease of the nervous system, where nerve cells in the brain and spinal cord that control voluntary movement gradually deteriorate, causing loss of muscle function and paralysis. The gradual loss of neurons leads to a paralysing effect on muscles used for breathing, which usually leads to death from respiratory failure. Treatment options for patients with ALS are extremely limited with current treatment revolving around supporting breathing.

Levosimendan works through binding to a protein called troponin C, which sensitises cardiac and skeletal muscles to calcium and increases their force of contraction. This increased force of contraction is thought to increase diaphragm function and support respiratory dysfunction. Levosimendan is given as an oral capsule and if licensed, it will offer a treatment option for patients with ALS, potentially delaying the need for mechanical ventilation support.

PROPOSED INDICATION

Levosimendan for the treatment of respiratory dysfunction in adult patients with amyotrophic lateral sclerosis (ALS).[a,1-4]

TECHNOLOGY

DESCRIPTION

Levosimendan (ODM-109) is a calcium sensitizer being developed for the treatment of respiratory dysfunction in patients with ALS. Levosimendan operates through binding selectively to troponin C, sensitising cardiac and skeletal muscles to calcium, leading to an increase in the force of contraction.[5] Effects of levosimendan increasing diaphragm function suggest a possible new application in improving respiratory function in patients with amyotrophic lateral sclerosis (ALS).[6]

Levosimendan is in phase III clinical development for the treatment of respiratory dysfunction in patients diagnosed with amyotrophic lateral sclerosis (ALS). In the phase III clinical trial (NCT03505021; REFALS) patients receive levosimendan 1mg oral capsules, once to twice a day, for a total treatment duration of 48 weeks. [2]

INNOVATION AND/OR ADVANTAGES

Treatment options for patients with ALS are extremely limited with no drugs currently available that significantly slow progression, and offer substantial clinical benefit.[7] Riluzole (Rilutek) is currently the only drug licensed for treating ALS in the UK. The licensed indication of riluzole is to extend life or the time to mechanical ventilation for individuals with ALS.[8]

Levosimendan may provide additional improved treatment options for ALS patients, through its' novel mechanism of sensitising cardiac and skeletal muscles to calcium, and increasing diaphragm force contraction. A previous study showed Levosimendan improved neuromechanical efficiency of human diaphragm function by 21% in healthy people.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Levosimendan is currently licensed as a 24-hour intravenous (IV) infusion for the short-term treatment of acutely decompensated severe chronic heart failure in several EU countries (excluding the UK).[10] Common side effects reported in this population for IV levosimendan include; hypotension, headache, atrial fibrillation, hypokalemia and tachycardia.[11]

Levosimendan is currently in investigator-initiated clinical studies for advanced chronic heart failure (Phase III) and for pulmonary hypertension (Phase II completed in June 2020, by Tenax Therapuetics).[12]

Levosimendan (administration as oral capsules) was designated as an orphan drug in the EU in February 2018 for the treatment of ALS.[13]

[a] Information provided by Orion Pharma (UK) Ltd on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Amyotrophic lateral sclerosis (ALS) is the most common type of motor neurone disease (MND), accounting for 65% to 85% of cases.[14] MND is a disorder that can affect adults of any age. It is most common in people aged 55–79 years, and onset below the age of 40 years is uncommon.[15] ALS is a progressive disease, where nerve cells in the brain and spinal cord that control voluntary movement gradually deteriorate, causing loss of muscle function and paralysis. The exact causes of ALS are unknown, however genetic and environmental factors are thought to be involved.[13]

There are two types of ALS - sporadic (sALS) and familial (fALS). The majority of ALS cases (>90%) are sALS, while around 5-10% are fALS. [16]

The symptoms of ALS depend on which muscles weaken first, and include loss of balance, loss of control of hand and arm movement, and difficulty speaking, swallowing and breathing. ALS usually starts in mid-life and men are more likely to develop the disease than women are. Poor respiratory function is a major source of disability, fatigue, morbidity and mortality in patients with ALS. Death occurring from respiratory failure, because of diaphragmatic weakness, typically occurs within 3–5 years of disease onset. [7,13,16]

Progressive disease often require patients to be placed on non-invasive mechanical ventilation support, in order to maintain respiratory function.[16]

CLINICAL NEED AND BURDEN OF DISEASE

It is estimated that there around 4,000 people living with MND in England and Wales at any one time.[15] There are no specific defined UK patient number figures for ALS, however a recent study by Gowland et al. pooled data from two regions of south-east England to generate robust incidence and prevalence rate estimates for ALS in the UK. Pooled data generated an overall incidence rate standardised to the UK population of 2.74 per 100,000 person-years in 2010, while the point prevalence was estimated at 8.30 per 100,000 in 2010. Future projections estimated an increase in the total number of people newly diagnosed with ALS per year in the UK from 1,415 in 2010 to 1,701 in 2020 and 2,635 in 2116.[17]

Hospital admissions data for England in 2018-2019 recorded 4,328 finished consultant episodes (FCE) for MND (ICD 10: G12.2), 2,612 hospital admissions, 875 day cases and 24,607 FCE bed days.[18]

Approximately 50% of patients with ALS die within 30 months of symptom onset, often from respiratory insufficiency,[19,20] however about 10% of patients may survive for more than a decade.[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is no cure for ALS, and as such, treatment revolves around maintaining patient's functional ability (e.g. respiratory function, nutritional intake and communication). Care for people with MND varies across England and Wales, with MND care centres and networks providing coordinated multidisciplinary care. A multidisciplinary team composing of; neurologists, specialist nurses, dieticians, physiotherapists, occupational therapists,

respiratory physiologists and speech and language therapists should be employed throughout the treatment. [15]

For ALS patients with respiratory dysfunction, non-invasive ventilation is provided to support breathing. Other treatment options for breathlessness recommended in the NICE guidelines include opioids and benzodiazepines.[15]

CURRENT TREATMENT OPTIONS

According to the NICE treatment pathway, current treatment options for respiratory dysfunction in patients with ALS include:[14,22,23]

- Riluzole to extend life or the time to mechanical ventilation or,
- Opioids or benzodiazepines to specifically manage breathlessness (these medicines do not have a UK MA for this indication, off-license prescription should follow the relevant guidelines) or,
- Non-invasive ventilation

PLACE OF TECHNOLOGY

If licensed, levosimendan will offer an additional treatment option for ALS patients to manage and delay the development of respiratory dysfunction, and potentially delay the need for mechanical ventilation support. It may be added to existing standard care.[b]

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**LEVALS; NCT02487407; Effects of ODM-109 on Respiratory Function in Patients With ALS. A Randomized, Double Blind, Placebo-controlled, Cross-over, 3-period, Multicenter Study With Open-label Follow-up Extension** **Phase II - completed** **Location(s): 4 EU countries (including UK)** **Actual study completion date: June 2017**
Trial design	Randomised, crossover assignment, quadruple blinded (participant, care provider, investigator, outcomes assessor)
Population	N=66, Subjects with diagnosis of laboratory supported probable, probable or definite ALS and an upright slow vital capacity (SVC) between 60-90% of the predicted value for age, height and sex at screening visit; aged 18 years and older.
Intervention(s)	Levosimendan 1mg oral capsule
Comparator(s)	Levosimendan oral placebo capsule
Outcome(s)	Pulmonary assessment using slow vital capacity (SVC). See trial record for full list of other outcomes
Results (efficacy)	Levosimendan did not achieve the primary endpoint of improving sitting SVC in ALS. Sitting SVC was not significantly different between the treatments. However, in post-hoc analysis, supine SVC indicated a dose-related treatment effect favouring levosimendan against placebo.[7]
Results (safety)	Levosimendan was generally well tolerated. However, headache and increased heart rate were more common during treatment compared to placebo.[7]

[b] Information provided by Orion Pharma (UK) Ltd on UK PharmaScan

Trial	**REFALS; NCT03505021; Effects of Oral Levosimendan (ODM-109) on Respiratory Function in Patients With ALS** **Phase III - ongoing** **Location(s):EU (including UK), US and other countries.** **Primary completion date: 30 August 2020**	**REFALS-ES; NCT03948178; Effects of Oral Levosimendan (ODM-109) on Respiratory Function in Patients With ALS: Open-Label Extension for Patients Completing Study 3119002** **Phase III (Extension Study to REFALS)** **Location: Spain** **Primary completion date: July 2022**
Trial design	Randomised, parallel assignment, quadruple blinded (participant, care provider, investigator, outcomes assessor)	Single group assignment, no masking (open label)
Population	N=450 (planned), Subjects with diagnosis of laboratory supported probable, probable or definite ALS and a sitting slow vital capacity (SVC) between 60-90% of the predicted value for age, height and sex at screening visit; aged 18 years to 120 years. Disease duration from symptom onset (defined as first muscle weakness or dysarthria) 12 – 48 months at baseline. If started prior to the study entry, patients are allowed to stay on stable dose of riluzole (and/or edaravone in the US).	N=450 (planned), Subjects who completed 48 weeks of treatment according to the REFALS study protocol; able to swallow study treatment capsules at the time of completing 48 weeks dosing in the REFALS study.
Intervention(s)	Levosimendan 1mg oral capsule once or twice daily	Levosimendan 1mg oral capsule once or twice daily
Comparator(s)	Levosimendan oral placebo capsule	No comparator
Outcome(s)	Primary outcome: Pulmonary assessment comparing the change in supine slow vital capacity (SVC) from baseline to 12 weeks vs placebo. CAFS (combined assessment of functionality and survival); ALSFRS-R; Time to respiratory event; Time to NIV/Tracheostomy/death See trial record for full list of other outcomes	Adverse Events (AE) ; Changes in pulse/heart rate values; Abnormal 12-lead ECG findings ALSFRS-R and others See trial record for full list of other outcomes
Results (efficacy)	-	-
Results (safety)	-	-

ESTIMATED COST

The cost of levosimendan is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Masitinib for treating amyotrophic lateral sclerosis (GID-TA10157). Expected publication date to be confirmed.
- NICE technology appraisal. Guidance on the use of Riluzole (Rilutek) for the treatment of Motor Neurone Disease (TA20). January 2001.
- NICE clinical guideline. Motor neurone disease: assessment and management (NG24). July 2019.
- NICE quality standard. Motor neurone disease (QS126). July 2016.
- NICE interventional procedures guidance (IPG593). September 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised rehabilitation for patients with highly complex needs (All ages). D02/S/a

OTHER GUIDANCE

- Royal College of General Practitioners and Motor Neurone Disease Association. Motor neurone disease: a guide for GPs and primary care teams. 2018.[24]

ADDITIONAL INFORMATION

REFERENCES

1 ClinicalTrials.gov. *Effects of ODM-109 on Respiratory Function in Patients With Amyotrophic Lateral Sclerosis (ALS). Trial ID*. 2015. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT02487407 [Accessed 10th April 2020].

2 ClinicalTrials.gov. *Effects of Oral Levosimendan (ODM-109) on Respiratory Function in Patients With ALS (REFALS). Trial ID*. 2018. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT03505021 [Accessed 6th April 2020].

3 ClinicalTrials.gov. *Effects of Oral Levosimendan on Respiratory Function in Patients With ALS: Open-Label Extension (REFALS-ES). Trial ID*. 2019. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT03948178 [Accessed 6th April 2020].

4 Corporation, O. *Orion's R&D Pipeline*. 2020. Available from: https://www.orion.fi/en/rd/orion-rd/pipeline/ [Accessed 6th April 2020].

5 Haikala, H., Levijoki J., Linden I. *Troponin C-mediated calcium sensitization by levosimendan accelarates the proportional development of isometric tension*. Journal of Molecular and Cellular Cardiology. 1995;27(10):2155-65. Available from: https://doi.org/10.1016/S0022-2828(95)91371-8

6 Holmstrom, K., Pollesello P., Garratt C. *Mechanism of action of the cardiovascular drug levosimendan in the management of amyotrophic lateral sclerosis.* Available from: https://www.orion.fi/globalassets/documents/rd/congress-posters/odm109/als_mnd-1-moa-poster_print.pdf [Accessed

7 Al-Chalabi, A., Shaw P., Leigh P., van den Berg L., Hardiman O., Ludolph A., et al. *Oral levosimendan in amyotrophic lateral sclerosis: a phase II multicentre, randomised, double-blind, placebo-controlled trial*. Journal of Neurology, Neurosurgery & Psychiatry. 2019;90:1165-70. Available from: http://dx.doi.org/10.1136/jnnp-2018-320288

8 British National Formulary (BNF). *Riluzole.* 2020. Available from: https://bnf.nice.org.uk/drug/riluzole.html#:~:text=NICE%20decisions&text=Riluzole%20is%20recommended%20for%20treating,arrangement%20involving%20the%20general%20practitioner. [Accessed 11th June 2020].

9 Doorduin, J., Sinderby C., Beck J., et a. *The calcium sensitizer levosimendan improves human diaphragm function*. Am J Respir Crit Care Med. 2012;185:90-5. Available from: http://dx.doi.org/10.1164/rccm.201107-1268OC

10 European Medicines Agency (EMA). *Levosimendan: List of nationally authorised medicinal products.* 2017. Available from: https://www.ema.europa.eu/en/documents/psusa/levosimendan-list-nationally-authorised-medicinal-products-psusa/00001858/201609_en.pdf [Accessed 11th June 2020].

11 Nieminen, M., Fruhwald S., Heunks L., Suominen P., Gordon A., Kivikko M., et al. *Levosimendan: current data, clinical use and future development*. Heart Lung Vessel. 2013;5(4):227-45. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3868185/

12 ClinicalTrials.gov. *Search Results for: Interventional Studies | Levosimendan | Phase 2, 3.* 2020. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=Intr&rslt=&age_v=&gndr=&intr=Levosimendan&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 11th June 2020].

13 European Medicines Agency (EMA). *EU/3/18/1980.* 2018. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3181980 [Accessed 7th April 2020].

14 National Insititute for Health and Care Excellence (NICE). *Guidance on the use of Riluzole (Rilutek) for the treatment of Motor Neurone Disease.* 2001. Available from: https://www.nice.org.uk/guidance/ta20/chapter/2-Clinical-Need-and-Practice [Accessed 9th April 2020].

15 National Insititute for Health and Care Excellence (NICE). *Motor neurone disease: assessment and management.* 2019. Available from: https://www.nice.org.uk/guidance/ng42/chapter/Context [Accessed 9th April 2020].

16 National Insititute of Neurological Disorders and Stroke. *Amyotrophic Lateral Sclerosis (ALS) Fact Sheet.* 2020. Available from: https://www.ninds.nih.gov/disorders/patient-caregiver-education/fact-sheets/amyotrophic-lateral-sclerosis-als-fact-sheet [Accessed 6th April 2020].

17 Gowland, A., Opie-Martin S., Scott K., Jones A., Mehta P., Batts C., et al. *Predicting the future of ALS: the impact of demographic change and potential new treatments on the prevalence of ALS in the United Kingdom, 2020–2116*. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2018;20(3-4):264-74. Available from: https://doi.org/10.1080/21678421.2019.1587629

18 NHS Digital. *Hospital Admitted Patient Care Activity 2018-19.* 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 9th April 2020].

19 Talbot, K. *Motor neuron disease*. Practical neurology. 2009;9(5):303. Available from: https://doi.org/10.1136/jnnp.2009.188151

20 Moura, M., Novaes M., Eduardo E., Zago Y., Freitas R., Casulari L. *Prognostic Factors in Amyotrophic Lateral Sclerosis: A Population-Based Study.* Plos one. 2015;10(10):e0141500-e. Available from: https://doi.org/10.1371/journal.pone.0141500.

21 Forsgren, L., Almay B., Wall S. *Epidemiology of motor neuron disease in northern Sweden*. Acta Neurologica Scandinavica. 1983;68(1):20-9. Available from: https://doi.org/10.1111/j.1600-0404.1983.tb04810.x

22 National Insititute for Health and Care Excellence (NICE). *Assessing and managing motor neurone disease.* 2020. Available from: https://pathways.nice.org.uk/pathways/motor-neurone-disease/assessing-and-managing-motor-neurone-disease#content=view-node:nodes-riluzole-for-treating-amyotrophic-lateral-sclerosis-motor-neurone-disease [Accessed 9th April 2020].

23 National Insititute for Health and Care Excellence (NICE). *Assessing and managing respiratory function in motor neurone disease.* 2020. Available from: https://pathways.nice.org.uk/pathways/motor-neurone-disease/assessing-and-managing-respiratory-function-in-motor-neurone-disease [Accessed 11th June 2020].

24 Motor Neurone Disease Association. *Motor neurone disease: a guide for GPs and primary care teams.* 2012. Available from: https://www.mndassociation.org/app/uploads/2012/04/px016-motor-neurone-disease-a-guide-for-gps-and-primary-care-teams.pdf [Accessed 11th June 2020].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.