NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Masitinib with Riluzole for amyotrophic lateral sclerosis

Company/Developer	AB Science

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 22761	NICE ID: 10728	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development

Summary

Masitinib in combination with riluzole is in clinical development for the treatment of patients with the amyotrophic lateral sclerosis (ALS), form of motor neurone disease (MND). 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. ALS is a debilitating and life-threatening disease. The gradual loss of neurons leads to a paralysing effect on muscles used for breathing, which usually leads to death from respiratory failure. There is currently no treatment to stop the progression of ALS.

Masitinib is a medicinal product, is administered orally and has been designed to reduce the activity of the defence cells of the brain and mast cells, a type of white blood cells. Through this reduction, masitinib is expected to reduce the damage and inflammation to the nerves that is caused by the activity of these cells thereby, slowing down the progression of symptoms in ALS patients. Riluzole is a drug orally administered to patients to extend life in ALS patients. If licenced, masitinib in combination with riluzole will provide an additional treatment option for adult patients with the ALS.

Proposed Indication

For the treatment of adults with amyotrophic lateral sclerosis (ALS).[1,2]

Technology

Description

Masitinib is an orally administered first in class tyrosine kinase inhibitor. Masitinib can exert a neuroprotective effect in both the central nervous system and peripheral nervous system through selective kinase inhibition with subsequent modulation of inflammatory and neurodegenerative processes.[3,4] Masitinib interferes with the activity, survival, and migration, of mast cells, and in this role has attracted attention for the treatment of neuroinflammatory and neurodegenerative disorders.[4] Microglia and mast cells are believed to play a role in the inflammation and damage to nerves in patients with ALS. By reducing their activity, masitinib is expected to reduce inflammation and damage to nerves, thereby slowing down the worsening of the patient's symptoms.[5]

Masitinib in combination with riluzole is currently in phase III clinical development for the treatment of adult patients with ALS (NCT03127267). In this trial, 3mg/kg/day of masitinib is administered orally, twice daily, with a dose escalation to 4.5mg/kg/day after 4 weeks in the first arm, and a further dose escalation to 6mg/kg/day after another 4 weeks in a second arm. Mastinib will be administered as an add-on to riluzole at 50mg twice daily (b.i.d).[2]

Key Innovation

The current treatment recommended by NICE for the treatment of ALS is riluzole. This is the only drug licenced for the treatment of ALS in the UK and is used to extend life,.[6] A phase II/III clinical trial, NCT02588677, found that masitinib exceeded the clinically meaningful target of slowing Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) progression rate by ≥20%, with further improvement possible when initiating treatment at a less severe stage of disease. It also showed significant improvement in terms of quality of live, respiratory function and time-delay in ALSFRS-R deterioration or death.[7]

If licenced, masitinib in combination with riluzole will offer an additional treatment for the symptoms of ALS.

Regulatory & Development Status

Masitinib in combination with riluzole does not currently have Marketing Authorisation in the EU/UK for any indication.

Masitinib is in phase II and III clinical development for the treatment of various conditions including:[8]

- Indolent systemic mastocytosis
- Colorectal cancer
- Ovarian cancer
- Alzheimer's disease

Masitinib has the following regulatory designation/awards:

- an orphan drug designation granted in the EU in August 2016 for the treatment of ALS[5]
- an orphan drug designation granted in the US in March 2015 for the treatment of ALS[9]

Patient Group

Disease Area and Clinical Need

MND is a rare disease that affects the brain and nerves, causing weakness that worsens over time.[10] ALS is a form of MND. 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.[5] There are two main types of ALS; sporadic and familial. Nearly all cases of ALS are sporadic, which means the disease occurs randomly with no clearly associated risk factors or family history of the disease. The exact causes of sporadic are unknown but are believed to include genetic and environmental factors. About 5-10% of all ALS cases are familial, which means that an individual inherits the disease from one parent who carries the disease-causing gene. Mutations found in more than a dozen genes have been associated with the onset familial ALS.[11]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.[5,11]

About 4,000 people in England have MND, of whom approximately 3,200 will have ALS.[12] In England, in 2020-21, there were 3,428 finished consultant episodes (FCE) for MND (ICD 10: G12.2), resulting in 2,129 hospital admissions and 14,700 FCE bed days.[13] ALS has a reported incidence of 1-2/100,000 person-years. 5000 people are estimated to have ALS in the UK at any one time; however, the true figure and geographical distribution, are unknown.[14] The proportion of people newly diagnosed with ALS annually in the UK is projected to rise from a baseline of 1,415 UK cases in 2010 to 1,701 in 2020 and 2,635 in 2116. The overall prevalence of ALS is predicted to increase from 8.58 per 100,000 persons in 2020 to 9.67 per 100,000 persons in 2116.[15]

Recommended Treatment Options

There is currently no cure for ALS and no effective treatment to halt or reverse the progression of the disease. Management of ALS consists of symptomatic and palliative care.[16] Riluzole 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.[6]

Clinical Trial Information

Trial	NCT03127267; Phase 3 Study to Compare the Efficacy and Safety of Masitinib in Combination With Riluzole Versus Placebo in Combination With Riluzole in the Treatment of Patients Suffering From Amyotrophic Lateral Sclerosis (ALS) **Phase –** Recruiting **Locations:** 8 EU countries and US **Primary completion date:** December 2023
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N=495 (estimated); Subjects aged 18 to 81 years with laboratory supported probable, clinically probable or definite ALS; Patient with a familial or sporadic ALS
Intervention(s)	Masitinib with riluzole (oral administration)

Comparator(s)	Match dose oral placebo given twice daily + riluzole at 50mg (oral administration)
Outcome(s)	Primary outcome: ALSFRS-R Change in Amyotrophic Lateral Sclerosis functional rating scale (ALSFRS)-Revised [Time frame: 48 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT02588677; Multicenter, Randomised, Double-blind, Placebo-controlled, Parallel Group, Phase 2/3 Study to Compare the Efficacy and Safety of Masitinib **Phase** – Completed **Location:** Spain **Actual completion date:** March 2018
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N=394 ; subjects aged 18 and older with familial or sporadic ALS, or diagnosed with probable of definite ALS; subjects treated with a stable dose of riluzole (100 mg/day) for at least 30 days prior to screening
Intervention(s)	Masitinib (3mg/kg/day) or masitinib 4.5 mg/kg/day + riluzole
Comparator(s)	Matched placebo (oral administration)
Outcome(s)	Primary outcome: Change in Amyotrophic Lateral Sclerosis functional rating scale (ALSFRS)-Revised [Time Frame: From baseline to week 48] See trial record for full list of other outcomes.
Results (efficacy)	The study showed statistically significant survival benefit of over 2 years and 47% reduced risk of death for patients receiving masitinib (4.5 mg/kg/day) as compared with placebo was observed for the enriched cohort of '⩾2 on each baseline ALSFRS-R item[17] Masitinib showed significant benefit in ΔALSFRS-R over placebo for the predefined primary efficacy population, exceeding the clinically meaningful target of slowing ALSFRS-R decline by ≥20% (27). Exploratory subgroup analyses indicated further improvement is possible when initiating treatment at a less severe stage of disease. Secondary endpoints also showed significant improvement in terms of quality-of-life (ALSAQ40), respiratory function, and time-delay in ALSFRS-R deterioration or death (time-to-event analysis).[7]
Results (safety)	-

Estimated Cost

The cost of masitinib is not yet known.

Riluzole is already marketed in the UK to extend life in patients with ALS; a pack of 56 x 50mg tablets costs £320.33, and treatment with Riluzole oral suspension 5 mg per 1 ml would cost £100.[18]

Relevant Guidance

NICE Guidance

- NICE Technology Appraisal guidance in development. Tofersen for treating amyotrophic lateral sclerosis caused by SOD1 gene mutations (GID-HST10050). TBC.
- NICE Technology Appraisal guidance. Guidance on the use of Riluzole (Rilutek) for the treatment of Motor Neurone Disease (TA20). January 2001.
- NICE guideline. Motor neurone disease: assessment and management (NG42). February 2016, updated July 2019.
- NICE quality standard. Motor neurone disease (QS126). July 2016.

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.[19]

Additional Information

AB Science did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

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