Health Technology Briefing
October 2023

SAR443820 for treating amyotrophic lateral sclerosis (ALS)

Company/Developer	Sanofi

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 34789	NICE ID: N/A	UKPS ID: 672641

Licensing and Market Availability Plans

Currently in phase II clinical trials.

Summary

SAR443620 is in phase II clinical development for the treatment of patients with amyotrophic lateral sclerosis (ALS), a form of motor neurone disease. ALS is a progressive disease where the nerve cells responsible for sending instructions to the muscles gradually deteriorate, leading to weakness, muscle wasting and paralysis. ALS is a debilitating and fatal disease. The initial symptoms of ALS can be varied but begin in the muscles that control speech and swallowing or in the hands, arms, legs or feet. Not all people with ALS experience the same symptoms or the same sequences or patterns of progression. However, progressive muscle weakness and paralysis are universally experienced. Currently, there is no cure for ALS and the treatments available have no profound effect on survival.

SAR443820 is a central nervous system (CNS)-penetrant technology, this unique ability allows it to cross the blood-brain barrier to reach the entire CNS. It works by inhibiting a protein called RIPK1, which can cause inflammatory nerve damage and brain cell death in patients with ALS. The orally administered SAR443820 may therefore prevent this activity from occurring. If licenced, SAR443820 will offer an additional treatment option for patients with ALS who currently have few effective therapies.

Proposed Indication

Treatment of adults with amyotrophic lateral sclerosis (ALS).[1]

Technology

Description

SAR443820 is a first-in-class, orally administered, central nervous system (CNS)-penetrant, selective receptor-interacting serine/threonine-protein kinase 1 (RIPK1) inhibitor. It has the ability to cross the blood-brain barrier (BBB), which allows the small molecule RIPK1 inhibitor to reach the entire CNS.[2] RIPK1 is a critical signalling protein in the TNF receptor pathway, which regulates inflammation and cell death in tissues throughout the body.[3] SAR443820 inhibits the RIPK1 signalling protein (pRIPK1) and thereby prevents RIPK1 activity from inflicting inflammatory damage and brain cell death.[2]

SAR443820 is currently in phase II clinical development for adults with ALS. In the phase II clinical trial (NCT05237284), participants receive oral SAR443820 twice daily for 24 weeks, followed by an extension period where all participants will receive SAR443820.[1]

Key Innovation

Currently, there is no cure for ALS and few treatments are available, none of which have a profound effect on survival.[4] A disease modifying drug, riluzole, is approved in the UK, however, it can only slow the progression for a few months and cannot reverse damage to motor neurons.[4-6] The ability of SAR443820 to cross the BBB and reach the entire CNS means it has the potential to be a key treatment option for ALS. In a Phase I clinical study amongst health volunteers, the drug was shown to be well tolerated with no significant treatment related adverse events, and target engagement of 80% median inhibition of pRIPK1 in blood at trough drug concentration was achieved.[3]

SAR443820 prevents damage to nerve cells and brain cell death caused by RIPK1 activities which causes inflammatory damage and brain cell death. If licenced, SAR443820, is expected to offer an additional treatment option for people with ALS who currently have a very few effective therapies available.

Regulatory & Development Status

SAR443820 does not currently have marketing authorisation in the EU/UK for any indication.
It is currently in phase II development for the treatment of multiple sclerosis.[7]

Patient Group

Disease Area and Clinical Need

ALS is a form of motor neurone disease (MND) and the most common type in the UK.[8] MND is a rare disease that affects the brain and nerves, causing weakness that worsens over time.[9] 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.[10] 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. 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 found to cause the familial ALS.[11] The initial symptoms of ALS can be quite varied. Symptoms can begin in the muscles that control speech and swallowing or in the hands, arms, legs or feet. Not all people with ALS experience the same symptoms or the same sequences or patterns of progression. However, progressive muscle weakness and paralysis are universally experienced. A gradual onset of progressive muscle weakness – which is generally painless – is the most common initial symptom in ALS. Other early symptoms vary but can include tripping, dropping things, abnormal fatigue of the arms and/or legs, slurred speech, muscle cramps and twitches, uncontrollable periods of laughing or crying and thinking and behavioural changes.[12] Following diagnosis someone diagnosed with ALS is expected to live from two to five years.[13]

ALS accounts for approximately 60-70% of the total MND cases.[14] The incidence of ALS ranges from 1.8 to 2.2 per 100,000 population, and the prevalence ranges from 4.0 to 4.7 per 100,000 population in the UK.[5] In England, 2021-22, there were 4,406 finished consultant episodes (FCE) and 2,694 admissions for MND (ICD-10 code G12.2), resulting in 21,826 FCE bed days and 1,029 day cases.[15]

Recommended Treatment Options

Management of ALS consists of symptomatic and palliative care.[5,16] Riluzole is the only recommended ALS treatment option by the National Institute for Health and Care Excellence (NICE).[5]

Clinical Trial Information

Trial	**HIMALAYA;** NCT05237284; 2021-004156-42; A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of SAR443820 in Adult Participants With Amyotrophic Lateral Sclerosis, Followed by an Open-label Extension (Part B) **Phase II:** Active, not recruiting. **Location(s):** Eight EU countries, UK, Canada, US, and other countries. **Primary completion date:** January 2024
Trial Design	Randomised, parallel assignment, triple blind
Population	N=304 (actual); male and female adults with diagnosis of possible, clinically probable ALS; clinically probable laboratory supported ALS, or clinically definite ALS according to the revised version of the El Escorial World Federation of Neurology criteria.
Intervention(s)	Twice daily oral dose of SAR443820
Comparator(s)	Placebo
Outcome(s)	Primary outcome measures: Change from baseline in the ALSFRS-R total score - Part A [Time frame: from baseline to week 24]

	Combined assessment of the function and survival (CAFS) score - Part B [Time frame: week 52] See trial record for other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of SAR443820 is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Masitinib with riluzole for treating amyotrophic lateral sclerosis (GID-TA11071). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Sodium phenylbutyrate–ursodoxicoltaurine for treating amyotrophic lateral sclerosis (GID-TA11264). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Tofersen for treating amyotrophic lateral sclerosis caused by SOD1 gene mutations (GID-HST10050). Expected July 2024
- 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 (NG42). February 2016. Updated: July 2019
- NICE quality standard. Motor neurone disease (QS126). July 2016. Last updated: July 2019.
- NICE interventional procedure guidance. Intramuscular diaphragm stimulation for ventilator dependent chronic respiratory failure caused by motor neurone disease (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.[17]

Additional Information

References

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