Health Technology Briefing
January 2025

Tolebrutinib for the treatment of primary progressive multiple sclerosis

Company/Developer	Sanofi

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30205	NICE ID: Not available	UKPS ID: 669155

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Tolebrutinib is currently in clinical development for the treatment of primary progressive multiple sclerosis (MS). MS is a condition where the body's immune system mistakenly attacks the nerves in the central nervous system (CNS) which consists of the brain and spinal cord. This damage prevents messages travelling from the CNS to other parts of the body. It causes a range of potential symptoms from pins and needles to difficulties with balance and walking. It can lead to increased mortality and is one of the most common causes of disability in younger adults. Progressive MS can occur in primary or secondary forms; primary progressive MS is a gradual worsening of symptoms from the initial primary symptoms. Current disease-modifying treatments are effective mainly in relapsing forms of MS; there is an unmet need for disease-modifying treatments for primary progressive MS.

Tolebrutinib is a medicinal product that inhibits (blocks the activity of) a protein called Bruton tyrosine kinase (BTK). BTK is critical for the activity of multiple types of immune cells which are involved in the progression of MS. By inhibiting BTK, tolebrutinib reduces the activity of the immune cells associated with MS and therefore targets the cause of the disease. Tolebrutinib is given as a daily oral tablet. If licenced, tolebrutinib will offer an additional treatment option for adult patients with MS.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Proposed Indication

The treatment of people with primary progressive multiple sclerosis (MS).[1]

Technology

Description

Tolebrutinib (SAR442168, PRN2246) is an oral central nervous system (CNS)-penetrant, and selective small molecule inhibitor of the Bruton tyrosine kinase (BTK) enzyme, which is critical for the activity of multiple immune cell types involved in multiple sclerosis (MS) progression.[2,3] BTK is essential for the survival and activation of B-cells, the cells responsible for making antibodies, which are major drivers of inflammation. But notably, this enzyme also regulates the activation of cells of the innate immune system, including microglia, which are thought to have a more prominent role in progressive forms of MS. By inhibiting BTK, tolebrutinib reduces the inflammatory activity that drives the progression of both relapsing and progressive forms of MS.[3]

Tolebrutinib oral tablet is currently in clinical development for the treatment of primary progressive MS. In the ongoing phase III trial (PERSEUS NCT04458051), tolebrutinib is given once daily as an oral tablet.[1]

Key Innovation

Currently, there is an unmet need for disease-modifying treatments for primary progressive MS.[4] Current disease-modifying treatments are partially effective in reducing relapses and slowing disease progression, but these treatments do not restore function and are effective mainly in relapsing forms of MS.[5] Tolebrutinib is an oral, CNS-penetrant, irreversible inhibitor of BTK, an enzyme expressed in B lymphocytes and myeloid cells including microglia, which are major drivers of inflammation in MS. The targeting of B cells and myeloid cells both outside and inside the CNS might have a greater—and perhaps synergistic—effect on neuroinflammation and demyelination than current disease-modifying therapies.[2]

In a phase IIb trial (NCT03889639), treatment with tolebrutinib demonstrated a dose-dependent reduction in the number of new gadolinium-enhancing (GdE) lesions and was well-tolerated among patients with RRMS and progressive forms of MS. Reduction of acute inflammation, combined with the potential to modulate the immune response within the CNS may alleviate symptoms of MS and outcomes for MS patients.[2] If licensed, tolebrutinib will offer an additional treatment option for adult patients with primary progressive MS.

Regulatory & Development Status

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

Tolebrutinib is in phase III/II clinical development for relapsing MS and secondary progressive MS.[6]

Patient Group

Disease Area and Clinical Need

MS is an acquired, chronic, immune-mediated, inflammatory condition of the CNS that can affect the brain, brainstem, and spinal cord. The inflammatory process causes areas of demyelination (damage to white matter), gliosis (scarring), and neuronal damage throughout the CNS.[7] It is a lifelong condition that can sometimes cause serious disability, although it can occasionally be mild. In many cases, it is possible to

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treat symptoms. Average life expectancy is slightly reduced for people with MS. It is most diagnosed in people in their 20s, 30s and 40s although it can develop at any age.[8] MS can have a wide range of symptoms including muscle spasms, stiffness and weakness, vision problems, abnormal sensations, mobility problems and pain. The symptoms are unpredictable. Some people's symptoms develop and worsen over time while for others, they come and go. The periods when these symptoms get worse are known as relapses, while the periods when the symptoms improve or disappear are known as remissions.[9] In primary progressive MS, symptoms gradually worsen and accumulate over several years, and there are no periods of remission, though people often have periods where their condition appears to stabilise.[8] About 10–15% of patients with MS present with gradually increasing neurological disability, a disorder known as primary-progressive MS.[10] The cause of MS is unknown — it is thought that acute then chronic immune-mediated inflammation is precipitated by an abnormal response to environmental triggers in people who are genetically predisposed.[11]

In 2018, the estimated prevalence of MS was 190 cases per 100,000 population, with 105,800 individuals in England. MS is more than twice as common in females than males, 272 versus 106 per 100,000 population.[12] In England, 2023-24, there were 66,569 finished consultant episodes (FCEs) and 64,036 admissions for multiple sclerosis (ICD-10 code G35) which resulted in 35,798 FCE bed days and 60,249 day cases.[13]

Recommended Treatment Options

NICE recommends ocrelizumab as an option for treating early primary progressive MS with imaging features characteristic of inflammatory activity in adults.[4]

Clinical Trial Information

Trial	**PERSEUS**, NCT04458051, **EudraCT** 2020-000645-14; A Phase 3, Randomized, Double-blind, Efficacy and Safety Study Comparing SAR442168 to Placebo in Participants With Primary Progressive Multiple Sclerosis (PERSEUS) **Phase III** – Active, not recruiting **Locations:** Nineteen EU countries, UK, USA, Canada, and other countries **Primary completion date:** July 2025	NCT06372145, **EudraCT** 2023-503631-18-01; An Interventional, Phase 3 Extension Study to Investigate Long-term Safety and Tolerability of Tolebrutinib in Participants With Relapsing Multiple Sclerosis, Primary Progressive Multiple Sclerosis, or Nonrelapsing Secondary Progressive Multiple Sclerosis **Phase III** – Recruiting **Locations:** Twenty-three EU countries, UK, USA, Canada, and other countries **Primary completion date:** April 2029
Trial Design	Randomised, parallel assignment, triple masking	Non-randomised, single group assignment, open label
Population	N (actual)=766; subjects with primary progressive MS; aged 18 to 55 years old.	N (estimated)=2,500; subjects with relapsing MS, primary progressive MS or non-relapsing secondary progressive MS; aged 18 years and older.
Intervention(s)	Tolebrutinib oral film-coated tablet	Tolebrutinib oral tablet (60mg)
Comparator(s)	Placebo oral film-coated tablet	Teriflunomide oral tablet (14mg)

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Outcome(s)	Primary outcome: time to onset of 3-month composite confirmed disability progression (cCDP) [Time frame: up to approximately 60 months] See trial record for full list of other outcomes	Primary outcomes: • Number of participants with adverse events (AEs) and serious AEs, AEs of special interest and AEs leading to permanent study intervention discontinuation [Time frame: from baseline until the end of the study approximately 3 years per participant] • Number of participants with potentially clinically significant abnormalities [Time frame: from baseline until the end of the study approximately 3 years per participant] See trial record for full list of other outcomes
Results (efficacy)	-	-
Results (safety)	-	-

Estimated Cost

The cost of tolebrutinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Ocrelizumab for treating primary progressive multiple sclerosis (TA585) June 2019.
- NICE clinical guideline. Multiple sclerosis in adults: management (NG220) June 2022.
- NICE quality standard. Multiple sclerosis (QS108). January 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies (NHS England Reference: 170079ALG). 2019.

Other Guidance

- Association of British Neurologists. Using disease-modifying treatments in multiple sclerosis: Association of British Neurologists (ABN) 2024 guidance. 2024.[14]
- Ghezzi, A. European and American Guidelines for Multiple Sclerosis Treatment. 2018.[15]
- ECTRIMS. Guideline on the pharmacological treatment of people with multiple sclerosis. 2018.[16]

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