NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
November 2023

Tolebrutinib for treating relapsing and progressive forms of multiple sclerosis

Company/Developer	Sanofi

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28046	NICE ID: 11845	UKPS ID: 664578 & 669154

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Tolebrutinib is currently in clinical development for the treatment of relapsing and progressive forms of multiple sclerosis (MS). MS is a chronic autoimmune condition that affects the brain and spinal cord. It can lead to increased mortality and is one of the most common causes of disability in younger adults. Relapsing remitting multiple sclerosis (RRMS) is the most common form and is characterised by episodes of acute worsening of function (relapsing) followed by partial or complete recovery (remitting). Progressive MS can occur in primary or secondary forms; primary progressive MS is a gradual worsening of symptoms from the initial primary symptoms. Secondary progressive MS is a stage which comes after RRMS and where symptoms, including new ones must have worsened for approximately six months. Common symptoms around the time of diagnosis are problems with eyesight, slowed thinking (cognitive symptoms), unusual feelings in the skin (such as pins and needles or numbness) and fatigue.

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.

Proposed Indication

Relapsing and secondary progressive forms of multiple sclerosis.[1,2]

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. 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.[3,4]

Tolebrutinib oral tablet is currently in clinical development for the treatment of relapsing and progressive forms of MS. In the ongoing phase III trials (NCT04410978, NCT04410991 and NCT04411641), tolebrutinib is given once daily as an oral tablet.[1,2,5]

Key Innovation

Tolebrutinib is a new medicinal product under investigation, demonstrated to be the only BTK inhibitor with sufficient CNS exposure and potency to modulate BTK signalling pathways within the CNS, as compared with other drugs.[6] Treatment with tolebrutinib reduced new active brain lesions in patients with relapsing-remitting MS (RRMS).[7]

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.[3] 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.

If licensed, tolebrutinib will offer an additional treatment option for adult patients with relapsing or progressive forms of MS.

Regulatory & Development Status

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

Tolebrutinib is currently also under investigation in a phase III trial for primary progressive MS.[8]

Patient Group

Disease Area and Clinical Need

MS is a chronic autoimmune condition that affects the brain and spinal cord, it can lead to increased mortality and is one of the most common causes of disability in younger adults, as it is most commonly diagnosed in people in their 20s, 30s and 40s.[9] In MS, the body's immune system continuously attacks the CNS, causing inflammation that damages the myelin sheath protecting the nerve fibres and nerve itself, causing disruption of signals from the brain. The nerve damage causes an increase in disability that can occur over time.[10] Relapsing-remitting MS is the most common form of MS, with 85% of patients presenting with this type; it is characterised by episodes of acute worsening of function followed by partial or complete recovery.[11] Some of the most common symptoms around the time of diagnosis are problems with eyesight, slowed thinking (cognitive symptoms) and unusual feelings in the skin (such as pins and needles or numbness). Fatigue is also very common and, together with other symptoms, impairs the quality of life of a person with MS.[9,12]

In England, MS estimated prevalence is 190 cases per 100,000 population, with 105,800 individuals in England diagnosed with the condition. On average 4,950 new cases of MS was diagnosed in England each year from 2009-2017, with a mean incidence rate of 9 per 100,000 population per year.[13] According to Hospital Episodes Statistics (HES) (ICD-10: G35) data in 2021/22, in England, there were 60,069 finished consultant episodes (FCEs), 57,462 admissions, resulting in 34,534 FCE bed days and 52,150 day cases with a primary diagnosis of MS.[14]

Recommended Treatment Options

For the treatment of acute relapse of MS, oral methylprednisolone for five days is offered.[15] The National Institute for Health and Care Excellence (NICE) recommends the following treatment options:[16]

- Diroximel fumarate (active RRMS)
- Ponesimod (active RRMS)
- Ofatumumab (active RRMS)
- Peginterferon beta-1a (RRMS)
- Ocrelizumab (active RRMS)
- Dimethyl fumarate (active RRMS)
- Teriflunomide (active RRMS)
- Alemtuzumab (highly active)
- Interferon beta-1a (RRMS)
- Interferon beta-1b (RRMS & secondary progressive MS)
- Glatiramer acetate (RRMS)
- Fingolimod (highly active)
- Siponimod (secondary progressive MS)
- Cladribine (highly active rapidly evolving syndrome & RRMS that has responded inadequately to disease modifying therapies)
- Natalizumab (highly active RRMS)

Clinical Trial Information

Trial	**HERCULES;** NCT04411641; EudraCT2020-000647-30**;** A Phase 3, Randomized, Double-blind, Efficacy and Safety Study Comparing SAR442168 to Placebo in Participants With Non-relapsing Secondary Progressive Multiple Sclerosis **Phase III -** Active, not recruiting

	Location(s): 17 EU countries, UK, United States, Canada and other countries (China) **Primary completion date:** August 2024
Trial Design	Randomised, parallel assignment, triple masked
Population	N=1131; participants with non-relapsing secondary progressive MS according to the 2017 revision of McDonald diagnostic criteria; aged 18 to 60 years old.
Intervention(s)	Tolebrutinib oral tablet
Comparator(s)	Placebo
Outcome(s)	Primary outcome: 6-month confirmed disability progression (CDP) [Time frame: Up to approximately 48 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**GEMINI 1**: NCT04410978; EudraCT: 2020-000637-41. Phase 3, Randomized, Double-blind Efficacy and Safety Study Comparing SAR442168 to Teriflunomide (Aubagio®) in Participants with Relapsing Forms of Multiple Sclerosis **Phase III** - Active, not recruiting **Location(s):** 13 EU countries, United States, Canada and other countries **Primary completion date:** April 2024
Trial Design	Randomised, parallel assignment, triple masked
Population	N=900; participants with relapsing MS (RMS) according to the 2017 revision of McDonald diagnostic criteria; aged 18 to 55 years old.
Intervention(s)	Tolebrutinib oral tablet
Comparator(s)	Teriflunomide oral tablet
Outcome(s)	Primary outcome: Annualised adjudicated relapse rate: Number of confirmed protocol defined adjudicated relapses [Time frame: Up to approximately 36 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	**GEMINI 2:** NCT04410991; EudraCT: 2020-000644-55. A Phase 3, Randomized, Double-blind Efficacy and Safety Study Comparing SAR442168 to Teriflunomide (Aubagio®) in Participants with Relapsing Forms of Multiple Sclerosis **Phase III -** Active, not recruiting **Location(s):** 12 EU countries, UK, United States, Canada and other countries **Primary completion date:** April 2024
Trial Design	Randomised, parallel assignment, triple masked
Population	N=900; participants with RMS according to the 2017 revision of McDonald diagnostic criteria; aged 18 to 55 years old.
Intervention(s)	Tolebrutinib oral tablet
Comparator(s)	Teriflunomide oral tablet
Outcome(s)	Primary outcome: Annualised adjudicated relapse rate: Number of confirmed protocol defined adjudicated relapses [Time frame: Up to approximately 36 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information		
Trial	NCT03889639. A Phase 2b Dose-finding Study for SAR442168, a Bruton's Tyrosine Kinase Inhibitor, in Participants with Relapsing Multiple Sclerosis **Phase II-** Completed **Location(s):** Six EU countries, United States, Canada and other countries **Primary completion date:** January 2020	NCT03996291. Long-term Extension Safety and Efficacy Study of SAR442168 in Participants with Relapsing Multiple Sclerosis Phase II- Active, not recruiting **Location(s)**: Five EU countries, United States, Canada and other countries **Primary completion date:** November 2024
Trial Design	Randomised, crossover assignment, double masked	Single group assignment, open label
Population	N=130; participants with RMS according to the 2017 revision of McDonald diagnostic criteria; aged 18 to 55 years old.	N=125; participants must have completed treatment in the DRI15928 study (NCT03889639)
Intervention(s)	Cohort 1: • 5mg oral tolebrutinib tablet then placebo	Double-blind period of continued treatment with the respective tolebrutinib dose.

	• 15mg oral tolebrutinib tablet then placebo • 30mg oral tolebrutinib tablet then placebo • 60mg 0ral tolebrutinib tablet then placebo Cohort 2: • Placebo then 5mg oral tolebrutinib • Placebo then 15mg oral tolebrutinib • Placebo then 30mg oral tolebrutinb • Placebo then 60mg oral tolebrutinib	Open-label period of 60mg tolebrutinib dose.
Comparator(s)	Matched oral placebo	None
Outcome(s)	Number of new Gd-enhancing T1 hyperintense lesions: Number of new Gd-enhancing T1 hyperintense lesions at the end of 12 weeks of SAR442168 treatment as detected by brain MRI [Time frame: Week 12 for Arms 1 - 4, Week 4 and Week 16 for Arms 5 – 8] See trial record for full list of other outcomes	Number of participants with adverse events (AEs) and serious adverse events (SAEs): [Time frame: Baseline to final follow-up visit (month 60 plus 8 weeks)] See trial record for full list of other outcomes
Results (efficacy)	• At treatment week 12, there was a dose-dependent reduction in the number of new gadolinium-enhancing lesions (mean lesions per patient: placebo, 1·03 [2·50]; 5 mg, 1·39 [3·20]; 15 mg, 0·77 [1·48]; 30 mg, 0·76 [3·31]; 60 mg, 0·13 [0·43]; p=0·03).[3] • 60 mg tolebrutinib was the most efficacious dose that was tested. Compared with placebo, the 60 mg dose resulted in 85% relative reduction in the number of new Gd enhancing lesions (primary endpoint), and 89% relative reduction in the number of new/enlarging T2 lesions (secondary endpoint).[3]	• At week 72, a low number of new Gd-enhancing lesions (mean counts: 0.62 [±1.06]) were observed for those in the 60/60-mg arm, where dosing had not changed. • For those in the 5/60-mg, 15/60-mg, and 30/60-mg arms, these lesions were reduced by mean counts of 0.68 (±0.98), 0.86 (±2.42), and 0.47 (±1.33), respectively, at weeks 48 and 72. • New/enlarging T2 lesion counts remained low for the 60/60-mg arm through week 24 and increased slightly at weeks 48 and 72.[18] • Slowly evolving lesion (SEL) volume, another MRI outcome measure, was 441 (IQR, 69-

		630), 468 (IQR, 102-1317), 675 (IQR, 150-1230), and 284 (IQR, 168-504) mm3 in the 5/60-, 15/60-, 30/60-, and 60/60-mg arms, respectively, at week 72. Most patients did not demonstrate changes in paramagnetic rim lesion counts.[18]
Results (safety)	129 of 130 (>99%) patients completed the trial per protocol. One SEA was reported; one patient in the 60 mg group was admitted to hospital because of a MS relapse. The most common adverse events were headache (13%), nasopharyngitis (9%), accidental overdose (9%). Over 12 weeks of tolebrutinib treatment, 1 patient from each of the 30 mg and 60 mg groups had elevated alanine transaminase concentrations that exceeded three times the upper limit of normal. No safety-related discontinuations or treatment-related deaths occurred.[3]	Most common AEs reported were headache (13%), COVID-19 (16%), nasopharyngitis (10%), upper respiratory tract infection (8%), and arthralgia (6%). There was no dose-dependent relationship observed for treatment-emergent AEs or SAEs in Part A (DRI15928/NCT03889639), and patients who switched to 60-mg tolebrutinib in Part B (NCT03996291) showed no new safety signals as well.[19]

Estimated Cost

The cost of tolebrutinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Diroximel fumarate for treating relapsing–remitting multiple sclerosis (TA794). June 2022.
- NICE technology appraisal. Ponesimod for treating relapsing–remitting multiple sclerosis (TA767). February 2022.
- NICE technology appraisal. Ozanimod for treating relapsing–remitting multiple sclerosis (TA706) June 2021.
- NICE technology appraisal. Ofatumumab for treating relapsing multiple sclerosis (TA699) May 2021.
- NICE technology appraisal. Siponimod for treating secondary progressive multiple sclerosis (TA656) November 2020.
- NICE technology appraisal. Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis (TA624) February 2020.
- NICE technology appraisal. Cladribine for treating relapsing–remitting multiple sclerosis (TA616) December 2019.

- NICE technology appraisal. Ocrelizumab for treating primary progressive multiple sclerosis (TA585) June 2019
- NICE technology appraisal. Ocrelizumab for treating relapsing–remitting multiple sclerosis (TA533) July 2018.
- NICE technology appraisal. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320) August 2014.
- NICE technology appraisal. Teriflunomide for treating relapsing–remitting multiple sclerosis (TA303) January 2014, Last updated: June 2014
- 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). NHS England; 2019.

Other Guidance

- Ghezzi. A. European and American Guidelines for Multiple Sclerosis Treatment. 2018.[20]
- ECTRIMS. Guideline on the pharmacological treatment of people with multiple sclerosis. 2018.[21]
- Association of British Neurologists: Guidelines for prescribing disease-modifying treatments in multiple sclerosis. 2015.[17]

Additional Information

References

1. Clinicaltrial.gov. *A Phase 3, Randomized, Double-blind Efficacy and Safety Study Comparing SAR442168 to Teriflunomide (Aubagio®) in Participants With Relapsing Forms of Multiple Sclerosis*. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04410978 [Accessed 10 February 2023].
2 ClinicalTrials.gov. *A Phase 3, Randomized, Double-blind, Efficacy and Safety Study Comparing SAR442168 to Placebo in Participants With Nonrelapsing Secondary Progressive Multiple Sclerosis Trial ID: NCT04411641*. 2020. Status: Active, Not Recruiting. Available from: https://clinicaltrials.gov/study/NCT04411641 [Accessed 18 October 2023].
3 Reich DS, Arnold DL, Vermersch P, Bar-Or A, Fox RJ, Matta A, et al. Safety and efficacy of tolebrutinib, an oral brain-penetrant BTK inhibitor, in relapsing multiple sclerosis: a phase 2b, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2021;20(9):729-38. Available from: https://doi.org/10.1016/s1474-4422(21)00237-4.
4 TODAY) MSN. *Tolebrutinib for Multiple Sclerosis: How does toelebrutinib work in MS*. Available from: https://multiplesclerosisnewstoday.com/tolebrutinib-multiple-sclerosis/ [Accessed 6 January 2023].
5 Clinicaltrial.gov. A Phase 3, Randomized, Double-blind Efficacy and Safety Study Comparing SAR442168 to Teriflunomide (Aubagio®) in Participants With Relapsing Forms of Multiple Sclerosis. https://www.clinicaltrials.gov/ct2/show/NCT04410991.
6 Sanofi. *New preclinical tolebrutinib data demonstrated superior brain penetration and potency*. 2022. Available from: https://www.sanofi.com/en/media-room/press-releases/2022/2022-02-24-14-01-00-2391553 [Accessed 6 January 2023].

7 Physician's Weekly. *Tolebrutinib Reduces New Active Brain Lesions in Relapsing MS*. Available from: https://www.physiciansweekly.com/tolebrutinib-reduces-new-active-brain-lesions-in-relapsing-ms [Accessed 6 January 2023].

8 Clinicaltrials.gov. *Tolebrutinib | Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Phase 2, 3*. Available from: https://clinicaltrials.gov/ct2/results?term=Tolebrutinib&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 10 January 2023].

9 National Health Service (NHS). *Multiple Sclerosis-Overview*. 2022. Available from: https://www.nhs.uk/conditions/multiple-sclerosis/ [Accessed 20 December 2022].

10 MS Society UK. *What is MS?- what happens in MS?* 2022. Available from: https://www.mssociety.org.uk/about-ms/what-is-ms [Accessed 20 December 2022].

11 McKay KA, Kwan V, Duggan T, Tremlett H. Risk Factors Associated with the Onset of Relapsing-Remitting and Primary Progressive Multiple Sclerosis: A Systematic Review. *BioMed Research International*. 2015;2015:817238. Available from: https://doi.org/10.1155/2015/817238.

12 Multiple Sclerosis Trust. *Relapsing remitting MS-What are the symptoms of relapsing remitting MS?* 2022. Available from: https://mstrust.org.uk/a-z/relapsing-remitting-ms#am-i-having-a-relapse [Accessed 20 December 2022].

13 GOV.UK. *Multiple sclerosis: prevalence, incidence and smoking status-data briefing*. 2020. Available from: https://www.gov.uk/government/publications/multiple-sclerosis-prevalence-incidence-and-smoking-status/multiple-sclerosis-prevalence-incidence-and-smoking-status-data-briefing [Accessed 22 February 2023].

14 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22. Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 5 December 2023].

15 National Institute of Health and Care Excellence (NICE). *Multiple sclerosis in adults: management*. Available from: https://www.nice.org.uk/guidance/ng220/chapter/Recommendations#other-treatments [Accessed 5 December 2023].

16 National Institute of Health and Care Excellence (NICE). *Multiple sclerosis: products on multiple sclerosis*. Available from: https://www.nice.org.uk/guidance/conditions-and-diseases/neurological-conditions/multiple-sclerosis/products?ProductType=Guidance&Status=Published [Accessed 5 December 2023].

17 Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Practical Neurology*. 2015;15(4):273-9. Available from: https://doi.org/10.1136/practneurol-2015-001139.

18 Reich D, Traboulsee A, Syed S, Dukovic D, Turner T, Arnold D. MRI Outcomes from the Long-term Extension Study of Tolebrutinib in Patients with Relapsing Multiple Sclerosis: 18-Month Results (P1-1.Virtual). *Neurology*. 2022;98(18 Supplement):2577. Available from MRI Outcomes from the Long-term Extension Study of Tolebrutinib in Patients with Relapsing Multiple Sclerosis: 18-Month Results (P1-1.Virtual) | Neurology

19 Oh J, Syed S, Orogun L, Dukovic D, Fox R. Safety and Clinical Efficacy Outcomes From the Long-term Extension Study of Tolebrutinib in Patients With Relapsing Multiple Sclerosis: 18-Month Results (S14.003). *Neurology*. 2022;98(18 Supplement):1648. Available from: Safety and Clinical Efficacy Outcomes From the Long-term Extension Study of Tolebrutinib in Patients With Relapsing Multiple Sclerosis: 18-Month Results (S14.003) | Neurology

20 Ghezzi A. European and American Guidelines for Multiple Sclerosis Treatment. *Neurology and Therapy*. 2018;7(2):189-94. Available from: https://doi.org/10.1007/s40120-018-0112-1.

21 Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *European Journal of Neurology*. 2018;25(2):215-37. https://onlinelibrary.wiley.com/doi/abs/10.1111/ene.13536.

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