Health Technology Briefing
April 2023

Evobrutinib for treating relapsing multiple sclerosis

Company/Developer	Merck Serono Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 21638	NICE ID: 11864	UKPS ID: 666338

Licensing and Market Availability Plans

Currently in phase II and III clinical trials.

Summary

Evobrutinib is in clinical development for the treatment of relapsing multiple sclerosis (RMS). Multiple sclerosis (MS) is a autoimmune disease that impacts the brain, spinal cord, and optic nerves, which make up the central nervous system (CNS). The cause of MS is not fully clear, but in MS, the immune system attacks the CNS which causes damage to the nerves. RMS is the most common form of MS and it is where you have relapses (symptoms getting worse), which can be followed by recovery ("remitting"). The most common symptoms reported in RMS include episodic tiredness, numbness, vision problems, muscle stiffness, bowel and bladder problems, and problems with cognition (learning and memory or information processing). There is no cure for MS. The overall aim of treatment is to manage symptoms to improve quality of life. Treatment is aimed at reducing the frequency and duration of relapses and at preventing or slowing disability.

Evobrutinib is an oral, highly selective inhibitor of Bruton's Tyrosine Kinase (BTK) which is important in the development and functioning of various immune cells. BTK inhibition is thought to suppress cells producing a type of protein called autoantibodies which are protein molecules that attack an individual's immune system, hence this inhibition may be therapeutically useful in certain autoimmune diseases such as MS. Evobrutinib will be administered as an oral tablet. If approved, evobrutinib will provide an additional treatment option for patients with RMS.

Proposed Indication

The proposed indication was confidential at the time of writing this briefing.

Technology

Description

Evobrutinib (M2951) is an oral, highly selective inhibitor of Bruton's Tyrosine Kinase (BTK) which is important in the development and functioning of various immune cells including B lymphocytes and macrophages. Evobrutinib is designed to inhibit primary B cell responses such as proliferation and antibody and cytokine release, without directly affecting T cells. BTK inhibition is thought to suppress autoantibody-producing cells, which preclinical research suggests may be therapeutically useful in certain autoimmune diseases.[1]

Evobrutinib is clinical development for the treatment of RMS. In the phase III clinical trials (evolutionRMS 1; NCT04338022, evolutionRMS 2; NCT04338061), evobrutinib will be administered orally twice daily.[2,3]

Key Innovation

Evobrutinib has the potential to become an efficacious treatment option for RMS by addressing both peripheral and central drivers of inflammation through inhibition of BTK signalling in B cells as well as microglia. The dual-faceted approach of evobrutinib may offer better control of silent progression of the disease in between attacks on top of strong relapse control in people living with RMS. Data from the phase II clinical trial (NCT02975349) demonstrated that annualised relapse rates (ARR) remained low and Expanded Disability Status Scale (EDSS) scores were stable in people with RMS treated with evobrutinib through more than three and half years. This is the first time that evidence of sustained efficacy out to three and a half years could be shown with a BTK inhibitor in RMS.[4] Evobrutinib was also the first BTK inhibitor to show impact on brain lesions associated with chronic inflammation and tissue loss from the Phase II clinical trial (NCT02975349). Evobrutinib reduced slow expanding lesions (SELs) volume in a dose-dependent manner, relative to placebo. Progressive accumulation of irreversible neural tissue damage and axonal loss as measured by SELs may be predictive of long-term clinical progression.[5] If approved, evobrutinib will be the first BTK inhibitor approved for the treatment of any form of multiple sclerosis (MS).[4,6]

Regulatory & Development Status

Evobrutinib does not currently have Marketing Authorisation in the EU/UK for any indication.

Evobrutinib was previously studied in phase II development trials for the treatment of rheumatoid arthritis.[7]

Patient Group

Disease Area and Clinical Need

MS is a disease that impacts the brain, spinal cord and optic nerves, which make up the central nervous system (CNS) and controls everything we do. The exact cause of MS is unknown, but we do know that something triggers the immune system to attack the CNS. The resulting damage to myelin, the protective layer insulating wire-like nerve fibres, disrupts signals to and from the brain. This interruption of communication signals causes unpredictable symptoms such as numbness, tingling, mood changes, memory problems, pain, fatigue, blindness and/or paralysis.[8] Relapsing-remitting MS (RRMS) is the most common disease type and it shows clearly defined attacks of new or increasing neurologic symptoms.

These attacks are also called relapses or exacerbations. They are followed by periods of partial or complete recovery, or remission. In remissions, all symptoms may disappear or some symptoms may continue and become permanent. However, during those periods, the disease does not seem to progress. Secondary progressive MS (SPMS) follows the initial relapsing-remitting disease type. Some people diagnosed with RRMS eventually go on to have a secondary progressive type, in which neurologic function worsens progressively or disability accumulates over time.[9] The most common symptoms reported in RRMS include episodic bouts of fatigue, numbness, vision problems, spasticity or stiffness, bowel and bladder problems, and problems with cognition (learning and memory or information processing). People with progressive forms of MS are more likely to experience gradually worsening problems with walking and mobility, along with whatever other symptoms they may have.[10] Scientists believe that a combination of factors trigger the disease. Studies support the opinion that MS is caused when people with the right combination of genes are exposed to some trigger in the environment. Research also suggests that ethnicity and geography play a role.[11] Factors that can potentially increase risk of relapses include stress, certain infections and low vitamin D levels.[12]

In the UK, there are over 130,000 people living with MS. Nearly 7,000 people are newly diagnosed with MS each year. Women are twice as likely to get MS as men; in 2022 the MS Society estimated that, of people living with MS in the UK, 73% are female and 27% are male. They also estimated that 107,300 people in England (1 in 500 people) had MS.[13] Around 85% of people with MS are diagnosed with RRMS.[12] Applying this statistic, it can be estimated that around 91,205 people in England had RRMS in 2022.[12,13] In England (2021-22), there were 60,069 finished consultant episodes (FCEs) and 57,462 admissions for a primary diagnosis of MS (ICD-10 code G35.X), which resulted in 52,150 day cases and 34,534 FCE bed days.[14]

Recommended Treatment Options

There is no cure for multiple sclerosis. The overall aims of treatment are to modify the course of the disease and manage symptoms, to improve quality of life. Current treatments are aimed at reducing the frequency and duration of relapses and at preventing or slowing disability. Under specialist care, disease-modifying drugs such as anti-lymphocyte monoclonal antibodies, antimetabolites, immunomodulators, immunostimulants, and interferons may be used for the treatment of relapsing-remitting multiple sclerosis.[15]

The National Institute for Health and Care Excellence (NICE) recommends the following treatment option for relapsing-remitting MS:[16,17]

- Diroximel fumarate
- Ponesimod
- Ofatumumab
- Alemtuzumab
- Peginterferon beta-1a
- Cladribine
- Ocrelizumab
- Dimethyl fumarate
- Teriflunomide
- Fingolimod
- Natalizumab
- Interferon beta-1a
- Interferon beta-1b (Extavia)

- Glatiramer acetate

Clinical Trial Information	
Trial	**evolutionRMS 1; NCT04338022; EudraCT-2019-004972-20;** A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared With Teriflunomide, in Participants With Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety (evolutionRMS 1) **Phase III –** Active, not recruiting **Location(s) –** 15 countries in EU, UK, USA, Canada and other countries **Primary completion date –** September 2023
Trial Design	Randomised, parallel assignment, quadruple-masked
Population	N = 1124 (actual); Participants are diagnosed with RMS (RRMS or SPMS with relapses); 18 Years to 55 Years
Intervention(s)	Evobrutinib, orally, twice daily
Comparator(s)	Teriflunomide, orally, once daily
Outcome(s)	**Primary outcome measures:** • Annualized Relapse Rate (ARR) [time frame: up to 156 weeks] • OLE Period: Number of participants with adverse events and serious adverse events (SAE)s [time frame: baseline OLE up to 96 weeks] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**evolutionRMS 2; NCT04338061; EudraCT-2019-004980-36;** A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared With Teriflunomide, in Participants With Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety (evolutionRMS 2) **Phase III –** Active, not recruiting **Location(s) –** 15 countries in EU, USA, Canada, and other countries **Primary completion date** – September 2023
Trial Design	Randomised, parallel assignment, quadruple-masked
Population	N = 1124 (actual); Participants are diagnosed with RMS (RRMS or SPMS with relapses); 18 Years to 55 Years
Intervention(s)	Evobrutinib, orally, twice daily
Comparator(s)	Teriflunomide, orally, once daily
Outcome(s)	**Primary outcomes measures:**

	• Annualized Relapse Rate (ARR) [time Frame: up to 156 weeks] • OLE Period: Number of participants with adverse events and serious adverse events (SAE)s [time frame: baseline OLE up to 96 weeks] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT02975349; A Randomized, Double-Blind, Placebo-Controlled Phase II Study of M2951 With a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients With Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity. **Phase II –** Active, not recruiting **Location(s) –** 6 countries in EU **Primary completion date –** January 2018
Trial Design	Randomised, parallel assignment, double-masked
Population	N = 267 (actual); Participants with a diagnosis of relapsing multiple sclerosis (may include participants with SPMS with superimposed relapses provided they meet the other criteria); 18 Years to 65 Years
Intervention(s)	• Evobrutinib 25mg orally, once daily up to week 48 or from week 24 to 48 weeks. • Evobrutinib 75mg orally once or twice daily up to week 48
Comparator(s)	• Tecfidera (Dimethyl Fumarate); 120mg hard capsule twice daily for 7 days then 240mg hard capsule twice daily for duration of treatment (48 weeks) or matched placebo for 24 weeks
Outcome(s)	**Primary outcome measures:** • Total number of gadolinium-enhancing T1 lesions [time frame: week 12 to week 24] See trial record for full list of other outcomes.
Results (efficacy)	The mean (±SD) total number of gadolinium-enhancing lesions during weeks 12 through 24 was 3.85±5.44 in the placebo group, 4.06±8.02 in the evobrutinib 25-mg group, 1.69±4.69 in the evobrutinib 75-mg once-daily group, 1.15±3.70 in the evobrutinib 75-mg twice-daily group, and 4.78±22.05 in the dimethyl fumarate (DMF) group. The baseline adjusted rate ratios for the total number of lesions over time as compared with placebo were 1.45 in the evobrutinib 25-mg group (P = 0.32), 0.30 in the evobrutinib 75-mg once-daily group (P = 0.005), and 0.44 in the evobrutinib 75-mg twice-daily group (P = 0.06). The unadjusted annualized relapse rate at week 24 was 0.37 in the placebo group, 0.57 in the evobrutinib 25-mg group, 0.13 in the evobrutinib 75-mg once-daily group, 0.08 in the evobrutinib 75-mg twice-daily group, and 0.20 in the DMF group. There was no

	significant effect of trial group on the change from baseline in the EDSS score. Elevations in liver aminotransferase values were observed with evobrutinib.[18]
Results (safety)	Evobrutinib 75-mg once-daily and twice-daily doses were associated with higher rates of adverse events, including grade 3 events, than the evobrutinib 25-mg dose or placebo. Higher evobrutinib doses were associated with a higher frequency of elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or lipase levels than in the other trial groups at 52 weeks. Most discontinuations from evobrutinib were caused by hepatobiliary disorders and changes in liver aminotransferase levels.[18]

Estimated Cost

The cost of evobrutinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal awaiting development. Ublituximab for treating relapsing–remitting multiple sclerosis (GID-TA11268). Expected date of issue to be confirmed.
- NICE technology appraisal awaiting development. Cladribine for treating relapsing multiple sclerosis (GID-TA11293). Expected date of issue to be confirmed.
- 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. Ofatumumab for treating relapsing multiple sclerosis (TA699). May 2021.
- NICE technology appraisal. Alemtuzumab for treating highly active relapsing remitting multiple sclerosis (TA312). May 2014, Last updated: March 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 relapsing–remitting multiple sclerosis (TA533). July 2018.
- NICE technology appraisal. Beta interferons and glatiramer acetate for treating multiple sclerosis (TA527). June 2018.
- NICE technology appraisal. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320). August 2014.
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- NICE technology appraisal. Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis (TA127). August 2007.
- NICE guideline. Multiple sclerosis in adults: management (NG220). June 2022.NICE quality standard. Multiple sclerosis (QS108). January 2016.

NHS England (Policy/Commissioning) Guidance

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Other Guidance

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Additional Information

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