NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
September 2022

Ublituximab for treating multiple sclerosis

Company/Developer	TG Therapeutics

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 12602	NICE ID: 11795	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Ublituximab is in development for the treatment of relapsing forms of multiple sclerosis (MS). MS is an autoimmune condition in which inflammation damages the protective insulation around nerves as well as the nerves themselves. MS can affect the brain and spinal cord, causing a wide range of potential symptoms, including problems with vision, arm or leg movement, sensation, or balance. The exact cause of MS is unclear, but it is thought that a combination of genetic and environmental factors are involved. Relapsing-remitting MS (RRMS) is the most common form, where the patient has attacks (relapses) between periods with few or no symptoms (remissions). There is currently no cure for MS, and there remains an unmet need for more treatments that are effective at reducing relapse rates.

Ublituximab is an intravenously administered monoclonal antibody (a type of protein) designed to recognise and attach to a unique part of a target protein called CD20, found on the surface of certain types of white blood cells (called B-cells). These white blood cells play a role in MS by attacking the protective insulation around the nerves in the brain and spinal cord, causing inflammation and damage. By targeting the B-cells, ublituximab helps to reduce their activity and thereby relieves symptoms or slows down the worsening of the disease. If licensed, ublituximab will provide an additional treatment option that reduces the relapse rate in patients with relapsing forms of MS.

Proposed Indication

Relapsing forms of multiple sclerosis (MS).[1]

Technology

Description

Ublituximab (TG-1101) is an investigational glycoengineered monoclonal antibody that targets a unique epitope on CD20-expressing B-cells. When ublituximab binds to the B-cell it triggers a series of immunological reactions (including antibody-dependent cellular cytotoxicity [ADCC] and complement dependent cytotoxicity [CDC]), leading to destruction of the cell.[2] MS is a demyelinating disease of the central nervous system, thought to be mediated by myelin-specific CD4+ T cells. B cell depletion has proven to be an effective therapy for MS, but the mechanism is not well understood. Data suggests that loss of B cells as antigen presenting cells is a major mechanism of action for the beneficial effects of CD20 antibody therapy in MS.[3]

Ublituximab is currently in clinical development for the treatment of relapsing forms of MS. In the phase III clinical trials (ULTIMATE I, NCT03277261; ULTIMATE II, NCT03277248) patients were given ublituximab as an intravenous (IV) infusion, 150mg over four hours on day one followed by 450 mg over one hour on days 15, 168 (week 24), 336 (week 48) and 504 (week 72) along with the oral placebo tablet, once daily (QD) from day one up to the last day of week 95.[1,4]

Key Innovation

Ublituximab has a unique epitope that is not targeted by other anti-CD20 monoclonal antibodies.[5] Targeting CD20 using monoclonal antibodies has proven to be an important therapeutic approach for the management of autoimmune disorders, which are driven by the abnormal growth or function of B-cells. Ublituximab is glycoengineered to lack certain sugar molecules normally expressed on the antibody. Removal of these sugar molecules has been shown to enhance the potency of ublituximab, especially the ADCC activity.[2]

In the phase III trials, ULTIMATE I, 86.7% vs 75.2% and in ULTIMATE II, 87.5% vs 73.5% of patients were free of relapse with ublituximab vs teriflunomide, respectively, at 96 weeks.[6]

If licensed, ublituximab will provide an additional treatment option that reduces the relapse rate in patients with relapsing forms of MS.

Regulatory & Development Status

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

Ublituximab monotherapy is also in phase I/II development for relapsed or refractory B-cell non-Hodgkin lymphoma, chronic lymphocytic leukaemia (CLL) and other types of lymphoma.[7]

Patient Group

Disease Area and Clinical Need

MS is an acquired, chronic, immune-mediated, inflammatory condition of the central nervous system (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. The onset of MS is typically in young adulthood.[8] Symptoms vary widely from person to person and the main

symptoms include fatigue, difficulty walking, vision problems, problems controlling the bladder, numbness or tingling, muscle stiffness and spasms, problems with balance and coordination, and problems with thinking, learning and planning.[9] 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.[10] Relapsing-remitting MS (RRMS) is the most common pattern of MS. RRMS is characterised by episodes or exacerbations of symptoms (relapses), followed by recovery (remissions) and periods of stability.[8]

The estimated prevalence of MS is 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.[11] In England (2020-21), there were 47,489 finished consultant episodes (FCEs) and 45,308 admissions for multiple sclerosis (ICD-10 code G35) which resulted in 26,417 FCE bed days and 41,440 day cases.[12]

Recommended Treatment Options

The following treatments are currently recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of relapsing MS:[13]

- Diroximel fumarate
- Ponedimod
- Ozanimod
- Ofatumumab
- Alemtuzumab
- Peginterferon beta-1a
- Cladribine
- Ocrelizumab
- Dimethyl fumarate
- Teriflunomide
- Fingolimod
- Natalizumab

Clinical Trial Information

Trial	**ULTIMATE I**, NCT03277261, 2017-000638-75; Phase III: Ublituximab In Multiple Sclerosis Treatment Effects **Phase III** – Completed **Location(s):** 2 EU countries, UK, USA and other countries **Study completion date:** November 2020	NCT04130997, 2019-003625-16; An Open Label Extension Study of Ublituximab in Subjects With Relapsing Multiple Sclerosis **Phase III** – Enrolling by invitation **Location(s):** 3 EU countries, USA and other countries **Primary completion date:** October 2023
Trial Design	Randomised, double-blinded, active-controlled	Single group assignment, open-label
Population	N=549 (actual); diagnosis of relapsing multiple sclerosis; active disease; aged 18 to 55 years	N=900 (planned); completed the 96-week double-blind TG1101-RMS301 (NCT03277261) or TG1101-RMS302 (NCT03277248) study or complete the

		final week 208 visit of the TG1101-RMS201E (NCT03381170) study; aged 18 years and older
Intervention(s)	Ublituximab (IV) + placebo (oral)	Ublituximab (IV)
Comparator(s)	Teriflunomide (oral) + placebo (IV)	No comparator
Outcome(s)	**Primary outcome:** – Annualised relapse rate (ARR) [Time frame: up to 96 weeks] See trial record for full list of other outcomes	**Primary outcome:** – Annualised relapse rate (ARR) [Time frame: up to week 172] See trial record for full list of other outcomes
Results (efficacy)	See trial record	-
Results (safety)	See trial record	-

Trial	**ULTIMATE II**, NCT03277248, 2017-000639-15; Phase III: Ublituximab in Multiple Sclerosis Treatment Effects **Phase III** – Completed **Location(s):** 3 EU countries, UK, USA and other countries **Study completion date:** November 2020
Trial Design	Randomised, double-blinded, active-controlled
Population	N=545 (actual); diagnosis of relapsing multiple sclerosis; active disease; aged 18 to 55 years
Intervention(s)	Ublituximab (IV) + placebo (oral)
Comparator(s)	Teriflunomide (oral) + placebo (IV)
Outcome(s)	**Primary outcome:** – Annualised relapse rate (ARR) [Time frame: up to 96 weeks] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Trial	NCT02738775; A Placebo-Controlled Multi-Center Phase IIa Dose Finding Study of Ublituximab, a Third-Generation Anti-CD20 Monoclonal Antibody, in Patients With Relapsing Forms of Multiple Sclerosis **Phase II** – Completed **Location(s):** USA **Study completion date:** August 2018	NCT03381170; An Open Label Extension of the TG1101-RMS201 Trial, for Subjects Currently Enrolled in TG1101-RMS201 Treated With Ublituximab for Relapsing Forms of Multiple Sclerosis **Phase II** – Active, not recruiting **Location(s):** USA **Primary completion date:** November 2022

Trial Design	Randomised, crossover assignment, double-blinded	Single group assignment, open-label
Population	N=49 (actual); diagnosis of relapsing multiple sclerosis; active disease; aged 18 to 55 years	N=48 (actual); subjects currently enrolled in TG1101-RMS201 (NCT02738775) trial; have completed three infusions of ublituximab and have completed the scheduled assessments up to the final 48-week visit; aged 18 to 55 years
Intervention(s)	Ublituximab (IV)	Ublituximab (IV)
Comparator(s)	Placebo (IV)	No comparator
Outcome(s)	**Primary outcome:** – Responder rate of B-cell - depletion at week 4 [Time frame: week 4] See trial record for full list of other outcomes	**Primary outcome:** – Number of participants with treatment-related events as assessed by CTCAE V4.0 [Time frame: 96 weeks on therapy] See trial record for full list of other outcomes
Results (efficacy)	See trial record	-
Results (safety)	See trial record	-

Estimated Cost

The cost of ublituximab 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. Alemtuzumab for treating highly active relapsing remitting multiple sclerosis (TA312). 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.
- NICE technology appraisal. Teriflunomide for treating relapsing–remitting multiple sclerosis (TA303). June 2014.
- NICE technology appraisal. Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis (TA254). April 2012.
- 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

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

Other Guidance

- Ghezzi A. European and American Guidelines for Multiple Sclerosis Treatment. 2018.[14]
- Association of British Neurologists. Revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. 2015.[15]

Additional Information

TG Therapeutics 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

1 Clinicaltrials.gov. *Phase III: Ublituximab In Multiple Sclerosis Treatment Effects (ULTIMATE I STUDY). Trial ID: NCT03277261*. 2017. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT03277261 [Accessed 19 July 2022].

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4 Clinicaltrials.gov. *Phase III: Ublituximab in Multiple Sclerosis Treatment Effects (ULTIMATE II STUDY). Trial ID: NCT03277248*. 2017. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT03277248 [Accessed 22 July 2022].

5 Mukhtar H, Yasmeen U, Siddiqa S, Sarfraz Z, Sarfraz A. Outcomes of Ublituximab compared to Teriflunomide for relapsing multiple sclerosis: A meta-analysis. *Multiple Sclerosis and Related Disorders*. 2022;65:104002. Available from: https://doi.org/10.1016/j.msard.2022.104002.

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