Health Technology Briefing
April 2022

Natalizumab biosimilar for treating relapsing-remitting multiple sclerosis

Company/Developer	Sandoz Limited

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28559	NICE ID: 10619	UKPS ID: 665217

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Natalizumab biosimilar is being developed as a biosimilar medicine to the approved monoclonal antibody natalizumab and is proposed to be used to treat adult patients relapsing remitting multiple sclerosis (RRMS). Multiple sclerosis is an autoimmune condition where the body's immune system attacks the brain and nerves. RRMS is characterised by attacks of new or increasing neurological symptoms, with intermittent periods of partial or complete recovery. Biosimilar medicines are biological therapies which have no clinically meaningful differences in efficacy, quality, and safety compared to the reference biologic product. Biosimilars are competitively priced to compete with the original product allowing them to be more widely available to the patients who need them.

Natalizumab is a type of monoclonal antibody that blocks the body's immune cells from entering the central nervous system (brain, spine, and nerves), preventing them from attacking the patient's own cells. Natalizumab biosimilar is administered intravenously, once every four weeks. If licensed, Natalizumab biosimilar would offer clinicians and patients a potentially cheaper alternative to the reference natalizumab as a treatment option for patients with relapsing remitting MS. Currently in phase III clinical trials.

Proposed Indication

Single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:[1]

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) OR
- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI

Technology

Description

Natalizumab (PB006) is in development as a biosimilar to the humanised anti-α4-integrin monoclonal antibody natalizumab (Tysabri), which is indicated in the UK as a single disease modifying therapy in adults with highly active RRMS.[1] Natalizumab blocks the adhesion molecule a4-integrin which prevents lymphocytes from the blood travelling into the central nervous system (CNS), preventing them from causing damage to the myelin sheath and nerves.[2] A biosimilar is a medicine which has no clinically meaningful differences compared to the reference medicine in terms of quality, safety and efficacy, with the same mechanism of action.[3]

In the confirmatory phase III trial (NCT04115488), natalizumab biosimilar given via intravenous (IV) infusion (300mg every 4 weeks for a total of 12 doses) was compared with reference natalizumab in adult patients with RRMS who had at least one documented relapse within the past year.[4]

Key Innovation

Natalizumab has the clinical benefit of slowing disease and disability progression over time, with 75% of patients receiving natalizumab after two years exhibiting no evidence of disease activity.[5] Natalizumab biosimilar has been shown to match the efficacy and safety profile of reference natalizumab, but competitive pricing for the proposed biosimilar will allow wider patient access.[6,7]

Biological medicines such as natalizumab are currently the largest cost and cost growth areas in the NHS medicines budget but new commissioning framework by NHS England aims to drive an uptake in biosimilar medicines and ensure patients are given the choice of switching to a new product by their doctors; this change to biosimilar products aims to save the NHS £300m each year, enabling more patients to have access to other life-saving and life-enhancing treatments.[3]

Regulatory & Development Status

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

Patient Group

Disease Area and Clinical Need

Multiple Sclerosis (MS) is a chronic 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 20's or 30's.[8] MS is an autoimmune condition where the body's own immune

system starts attacking the CNS, causing inflammation that damages the myelin sheath protecting the nerve fibres and to the nerves themselves, resulting in disruption of signals from the brain.[9,10]

Relapsing and remitting MS is the most common form of MS with 80% of patients diagnosed with this type, and is characterised by repeated episodes of new or worsening symptoms which then improve over time but often don't disappear.[8] Active disease is defined as at least two clinically significant relapses occurring within the last 2 years; highly active disease is characterised by an unchanged/increased relapse rate or by ongoing severe relapses compared with the previous year, despite treatment with interferon beta. Rapidly-evolving severe relapsing-remitting MS is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.[11]

Symptoms of MS include fatigue, difficulty walking, vision problems, loss of bladder control, numbness or stiffness, balance and coordination problems, and cognitive impairment, all impairing the quality of life of a person with MS.[8]

Each year in the UK over 7,000 people are diagnosed with MS, with an average incidence rate of 286 women and 111 men per 100,000 people on average (2012-17).[12] The average life expectancy for patients with MS is 5-10 years lower than the average in the UK.[8] In England (2020-21), there were 47,489 finished consultant episodes (FCE) for MS (ICD-10 code: G35), with 45,308 hospital admissions that resulted in 41,440 day cases and 26,417 FCE bed days.[13] In England and Wales (2020) there were 1,346 deaths registered with MS as the underlying cause.[14]

Recommended Treatment Options

NICE currently recommends the following therapies for the treatment of highly active relapsing remitting multiple sclerosis:[15]

- Natalizumab
- Fingolimod
- Alemtuzumab

Clinical Trial Information

Trial	**Antelope;** NCT04115488, 2018-004751-20; Efficacy and Safety of the Biosimilar Natalizumab PB006 in Comparison to Tysabri® in Patients With Relapsing-Remitting Multiple Sclerosis (RRMS) **Phase III** – Completed[a] **Location(s):** 2 EU countries and 5 other countries **Primary completion date:** March 2021
Trial Design	Randomised, parallel assignment, quadruple masked
Population	N= 264[b]; Subjects with relapsing-remitting MS; Aged 18 to 60 years old.
Intervention(s)	Natalizumab biosimilar, IV infusion of 300mg, every 4 weeks with a total of 12 doses

[a] Information provided by Sandoz Limited

Comparator(s)	Reference Natalizumab, IV infusion of 300mg every 4 weeks with a total of 12 doses
Outcome(s)	Primary outcome: evaluate and compare the efficacy of Biosim-NTZ with Ref-NTZ using the combined number of unique active (CUA) lesions (new gadolinium-enhancing T1-weighted lesions and new/enlarging T2-weighted lesions) from baseline up to Week 24 of treatment.[7] See trial record for full list of other outcomes
Results (efficacy)	The results of the primary efficacy analysis showed that Biosim-NTZ (n=131) had a similar efficacy to Ref-NTZ (n=133). The respective mean (standard deviation) number of CUA lesions at Week 24 was 1.4 (3.62) for Biosim-NTZ and 1.9 (3.94) for Ref-NTZ.[7] A least square mean difference of 0.17 (95% CI: −0.613, 0.944) confirmed equivalence between the biosimilar and reference products as it was within the pre-specified margins of ±2.1 based on previous MRI studies. The mean number of lesions at each MRI scan over the 24-week period were also similar and ranged from 1.2 to 1.4 in Biosim-NTZ-treated patients and from 1.6 to 1.9 in Ref-NTZ-treated patients.[b]
Results (safety)	The safety profiles and incidence rate of adverse events (AEs) were comparable between the Biosim-NTZ and Ref-NTZ arms. No cases of progressive multifocal leukoencephalopathy or deaths were reported for either group. Importantly, no new safety signals were observed in the Biosim-NTZ group.[7]

Estimated Cost

The cost of natalizumab biosimilar was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Aletuzumab for treating highly active relapsing remitting multiple sclerosis (TA312). March 2020.
- NICE technology appraisal. Cladribine for treating relapsing-remitting multiple sclerosis (TA616). December 2019.
- NICE technology appraisal. Fingolimod for treating 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 clinical guideline. Multiple sclerosis in adults: management (CG186). November 2019.
- NICE quality standard. Multiple sclerosis (QS108). January 2016.
- NICE interventional procedure guidance. Percutaneous venoplasty for chronic cerebrospinal venous insufficiency in multiple sclerosis (IPG640). January 2019.

NHS England (Policy/Commissioning) Guidance

[b] Information provided by Sandoz Limited

- NHS England. Urgent Clinical Commissioning Policy: Natalizumab induced progressive multifocal leukoencephalopathy in relation to immune reconstitution inflammatory syndrome in multiple sclerosis (all ages). NHS England/170040/P. December 2018.
- NHS England. Urgent Clinical Commissioning Policy: Alemtuzumab for treating relapsing-remitting multiple sclerosis – third cycle (all ages). NHS England/170075/P. August 2018.
- NHS England. Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS). NHS England/D04/P/b. May 2014.
- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (adult). D04/S/a.

Other Guidance

- ECTRIMS. Guideline on the pharmacological treatment of people with multiple sclerosis. 2018.[16]
- European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis. 2015.[17]

Additional Information

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