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Newcastle University

Health Technology Briefing
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Belimumab (subcutaneous injection) add-on for systemic lupus erythematosus in children aged 5 to 17 years old

Company/Developer	GlaxoSmithKline UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 35278	NICE ID: 11828	UKPS ID: 660001

Licensing and Market Availability Plans

Currently in phase II clinical development.

Summary

Belimumab (subcutaneous injection) is currently in clinical development as an add-on therapy for active systemic lupus erythematosus (SLE) in patients aged 5 to 17 years old. SLE is an autoimmune disease where the body's immune system attacks its own tissues and organs. Patients will often have periods where their symptoms flare-up and periods where their symptoms settle down. In children, SLE is more severe than in adults. Currently, conventional SLE treatments, such as corticosteroids and immunosuppressants, are known to have issues with efficacy and long-term toxicity.

Belimumab is a monoclonal antibody, a protein that has been designed to attach to and block a protein called BLyS which helps B lymphocytes to live longer. By blocking the action of BLyS, belimumab reduces the life span of B lymphocytes, thereby reducing the inflammation and organ damage that occur in SLE. Belimumab (intravenous infusion) is used as an add-on treatment for patients aged 5 years and older with active, autoantibody-positive SLE with a high degree of disease activity despite standard therapy. Belimumab administered as a subcutaneous injection (under the skin), compared to intravenous infusion, may be more beneficial to patients in terms of their quality of life. If licensed, belimumab SC will offer an additional treatment option for paediatric patients with SLE.

Proposed Indication

Add-on therapy for active systemic lupus erythematosus (SLE) in paediatrics aged 5 to 17 years old.[1]

Technology

Description

Belimumab (Benlysta) is a human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.[2]

Belimumab subcutaneous injection (SC) is currently in clinical development as an add-on therapy for active SLE in patients aged 5 to 17 years old. In the phase II clinical trial (NCT04179032), belimumab 200 mg/mL will be administered as SC injection in left or right thigh and the abdomen for 12 weeks, with the frequency of administration based on body weight.[1]

Key Innovation

Belimumab intravenous infusion (IV) is already licensed in the UK as add-on therapy for patients aged 5 years and older with active, autoantibody-positive SLE with a high degree of disease activity despite standard therapy.[2] SC injection, (compared to IV), is less time-consuming, and it takes less effort and time absent from work (or school for children) when self-administration is performed at home. Subcutaneous application systems are designed with smaller needle sizes, which may decrease pain during administration. Furthermore, administration at home reduces the risk of exposure to hospital-acquired infections. Subcutaneous application is expected to improve patient quality of life and provide support to patients who live far from a hospital or have difficulties travelling and parking in the vicinity of the hospital. This can also contribute to a lower financial burden.[3] This may lead to the findings that patients prefer SC over IV delivery.[3,4] If licensed, belimumab SC injection will offer an additional treatment option for paediatric patients with SLE.

Regulatory & Development Status

Belimumab (IV) is licensed in the EU/UK for the following indications:[2]

- as add-on therapy in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy
- in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis

Belimumab (SC) is licensed in the EU/UK for the following indications:[5]

- indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy
- in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis

Belimumab is in phase II and III clinical development for:[6]

- Antiphospholipid syndrome
- Cryoglobulinemia vasculitis
- Primary membranous nephropathy

- Chronic lymphoid leukemia
- Granulomatosis with polyangiitis
- Primary immune thrombocytopenia
- Systemic sclerosis
- Lupus nephritis
- Neuromyelitis optica spectrum disorders

Patient Group

Disease Area and Clinical Need

SLE is a chronic multisystem inflammatory autoimmune disease associated with impaired health-related quality of life.[7] In people with SLE, the immune system creates autoantibodies to attack the body's tissues. These form immune complexes which cause inflammation and damage – possibly affecting the organs and/or the joints in some SLE patients.[8] In people with SLE, cells that have undergone apoptosis are not cleared away properly. The relationship between this and the cause or features of SLE are unclear but researchers suggest that these dead cells may release substances that cause the immune system to react inappropriately and attack the body's tissues, resulting in the signs and symptoms of SLE.[9] Most people with SLE have mild disease characterised by episodes — called flares — when signs and symptoms get worse for a while, then improve or even disappear completely for a time. The signs and symptoms of SLE that people experience will depend on which body systems are affected by the disease. The most common signs and symptoms include: fatigue, fever, joint pain, stiffness and swelling, butterfly-shaped rash on the face, skin lesions that appear or worsen with sun exposure, fingers and toes that turn white or blue when exposed to cold or during stressful periods, shortness of breath, chest pain, dry eyes, headaches, confusion and memory loss.[10] The symptoms children with SLE may experience are very similar to adult symptoms, but they can be more severe in children.[11] Severe SLE causes life-threatening involvement to the heart, lungs, brain, bone marrow or kidneys and are more likely to cause irreversible damage accrual in the first years of disease.[12] The causes of SLE are unknown but are believed to be linked to environmental, genetic and hormonal factors.[13]

SLE disproportionately affects females and people from Black African, Caribbean, and Asian ancestries. SLE can often develop around puberty, after childbirth, during menopause and usually occurs in females between the ages of 15 to 55.[8] It is rare to get lupus before age 5 years.[14] In England, in 2021-2022, there were 6,434 admissions for SLE (ICD: 10 code M32) of which 487 were for children and adolescents aged 5-17 years old. This, as a proportion is 7.5% of the total burden of disease of SLE in England in 2021-2022. Finished consultant episode (FCE) bed days and day cases resulted in 7,516 and 5,361 respectively for SLE for all age groups across England. For 5-17 years old age group that would be 564 FCE bed days and 402 day cases based on the estimated proportion of the burden of disease for this age group.[15]

Recommended Treatment Options

The following treatments are recommended for juvenile SLE:[14]

- Corticosteroids
- Hydroxychloroquine
- Immunosuppressive medicinal products, such as azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide and rituximab

Clinical Trial Information

Trial	NCT04179032; A Multi-Center, Open-Label Trial to Evaluate the Pharmacokinetics, Safety, and Pharmacodynamics of Subcutaneously Administered Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Participants With Systemic Lupus Erythematosus (SLE) **Phase II –** Active, not recruiting **Location(s):** Three EU countries, USA, Argentina, Japan and Mexico **Primary completion date:** January 2023
Trial Design	Single group assignment, open-label
Population	N=30 (estimated); patients aged 5-17 years old who meet the 1997 American College of Rheumatology (ACR) criteria for the classification of SLE; active SLE; are on a stable SLE treatment regimen.
Intervention(s)	SC 200 mg/mL belimumab administered in left or right thigh and the abdomen for 12 weeks (part A). In Part B (optional), dosing of SC belimumab will continue at the same frequency or may require a change in frequency according to changes in participant's body weight for 40 weeks.
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Observed belimumab concentrations at Week 12 [time frame: at Week 12] • Estimated average concentration (Cavg) of belimumab at steady state [time frame: up to Week 60] • Estimated maximum concentration (Cmax) of belimumab at steady state [time frame: up to Week 60] • Estimated minimum concentration (Cmin) of belimumab at steady state [time frame: up to Week 60] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Belimumab is already marketed in the UK for the treatment of SLE; a 120mg vial costs £121.50 (hospital only) and a 400mg vial costs £405.00 (hospital only).[16]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Belimumab for treating active autoantibody-positive systemic lupus erythematosus (TA752). December 2021.

NHS England (Policy/Commissioning) Guidance

- No relevant guidance identified

Other Guidance

- Pediatric Rheumatology Association of Japan and the Pediatric Rheumatology Subcommittee in the Japan College of Rheumatology. Clinical practice guidance for childhood-onset systemic lupus erythematosus—secondary publication. 2022.[17]
- Marisa Klein-Gitelman. Systemic lupus erythematosus (SLE) in children: Treatment, complications, and prognosis. 2019.[18]
- Noortje Groot, Nienke de Graeff, Tadej Avcin et al. European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. 2017.[19]

Additional Information

References

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