

HEALTH TECHNOLOGY BRIEFING OCTOBER 2019

Belimumab for lupus nephritis

NIHRIO ID	27044	NICE ID	10200
Developer/Company	GlaxoSmithKline	UKPS ID	650659

Licensing and market availability plans

Currently in phase III clinical trials.

SUMMARY

Belimumab is in clinical development for the treatment of adults with active lupus nephritis (LN) who are uncontrolled on current standard of care. LN is a complication affecting kidney function brought on by systemic lupus erythematosus (SLE), a chronic autoimmune, inflammatory disease that affects different organs. Around a third of people suffering with SLE will develop LN. The kidney damage seen in LN occurs due to a person's immune cells (B Cells) attacking their own kidneys which causes inflammation and affects overall kidney function. Current treatment involves suppression of the immune system and management of symptoms, but it is not always effective. If left untreated, LN can lead to kidney failure which requires dialysis or a kidney transplant.

Belimumab is a monoclonal antibody which binds to a soluble B cell survival factor known as BlyS, thereby stopping the growth and activity of B cells. It is given by intravenous infusion and is intended to be added on to current standard of care therapies. Belimumab is currently approved as an add-on therapy for adult patients with SLE in the EU/UK and if licensed for LN, will offer a new targeted therapy that is able to treat patients who cannot tolerate the side effects related to the current standard of care.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Adult patients with active lupus nephritis (LN) who are uncontrolled on current standard of care.^{1,a}

TECHNOLOGY

DESCRIPTION

Belimumab (Benlysta) is a human IgG1 λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TSFSF13B). 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 Autoreactive B cells play a critical role in the severe inflammation and resulting tissue damage in LN patients and inhibition of these cells provides a new therapeutic option.³

Belimumab is currently in clinical development for the treatment of adult patients with active LN who are uncontrolled on current standard of care. In the phase III clinical trial (NCT01639339; BLISS-LN), participants received belimumab 10mg/kg by intravenous (IV) infusion plus standard therapy. Belimumab was administered on days 0, 14 and 28 and then every 28 days thereafter through week 100 of the double-blind treatment.¹

INNOVATION AND/OR ADVANTAGES

The current therapeutic options for LN range from corticosteroids to immunosuppressive treatments such as azathioprine, cyclophosphamide (CYC) and mycophenolate mofetil (MMF).^{3,4} Unlike current options, belimumab is able to target B lymphocytes specifically through BLyS inhibition, which disrupts critical development stages and homeostasis of B lymphocytes. B lymphocytes are the immune cells which produce the autoantibodies which play a central role in the LN pathogenesis. . This targeted approach to therapy can potentially address the unmet needs for patients who are unable to tolerate the side effects of the current standard of care.³

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Belimumab is currently licensed in the EU/UK as an 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.²

The most common side effects with belimumab in adults (seen in more than one in 10 patients) are bacterial infections such as bronchitis and urinary tract infection, and gastrointestinal disorders such as diarrhoea and nausea.²

Belimumab is in phase II and phase III clinical development for:⁵

- Primary Sjogren's syndrome
- In combination with rituximab for the treatment of SLE

^a Information provided by GlaxoSmithKline on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Lupus nephritis (LN) is a frequent renal complication of systemic lupus erythematosus (SLE) which occurs in 40-75% of SLE patients.⁴ SLE is a chronic, multifaceted, autoimmune disease which is characterised by loss of self-tolerance to nuclear autoantigens leading to lymphoproliferation, autoantibody production, immune complex disease and multi-organ tissue inflammation.^{3,6} LN occurs when there is renal involvement in the SLE disease course, which can range from low levels of proteinuria to acute glomerulonephritis and renal failure⁴.

LN is associated with high levels of morbidity, including renal failure, and some mortality in patients. The usual disease course of LN involves a number of flares of disease and subsequent periods of quiescence.⁷ Patients can experience symptoms related to glomerulonephritis such as oedema (swelling) mainly in the extremities or the eyes, foamy or red coloured urine, increased urination and high blood pressure. If untreated, LN causes permanent renal damage which may lead to end-stage renal disease (ESRD). If a patient develops ESRD, they would require regular dialysis or a kidney transplant.⁸

While the specific mechanisms of pathogenesis are still being elucidated, recent studies have shown that immune complex deposition, complement pathway activation and local inflammatory responses from renal cells play a role in LN development.⁷ Immune complex deposits in glomerular areas consisting of Immunoglobulin M, A and G are a diagnostic hallmark of LN and activate local proinflammatory effects in renal cells. This inflammation damages the kidney and can lead to secondary membranous glomerulonephritis and nephrotic syndrome. Additionally, immune complex deposition activates the complement system which directly causes renal inflammation and immunopathology. Alongside B lymphocytes, T lymphocytes and macrophage also play a role in pathogenesis by infiltrating the kidney and producing large amounts of proinflammatory cytokines such as IFN- α and IFN- β , which leads to further renal inflammation and damage.⁶

CLINICAL NEED AND BURDEN OF DISEASE

Gender is considered one of the strongest risk factors for the development of SLE. Around 90% of studies containing SLE patients contain all-female populations and the incidence of SLE in females is approximately 5.8 times higher than that of males (8.34 per 100,000 per year for females compared to 1.44 per 100,000 per year for males). In studies, incidence of SLE in females peaked during the ages of 40-49 years, while it was at a much later age for males (60-69 years).^{9,10}

In 2012, the prevalence of SLE was 97 per 100,000 people in the UK.¹⁰ Of these people, approximately 33% will develop LN throughout the disease period.¹¹ Based on the population estimates for England and Wales (Mid-2018), the number of expected adult patients with diagnosed lupus nephritis is 14,985.¹²

The company estimate the UK patient population range to be between 1,500 and 2,000 per 100,000^b

^b Information provided by GlaxoSmithKline on UK PharmaScan

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main goal for managing and treating LN looks to preserve long-term renal function, prevent flare of disease, avoid treatment-related side effects and improve patient quality of life. It is recommended that LN patients are treated in specialist healthcare centres by a nephrologist, lupologist, or experienced rheumatologist.¹³

Current treatment aims to diagnose patients with LN early and treat with corticosteroids and immunosuppressive medicinal products. In patients that do not respond to treatment and develop ESRD, it is possible to ameliorate symptoms with dialysis and/or renal transplantation.¹⁴

CURRENT TREATMENT OPTIONS

Current recommendations for treating LN patients is with mycophenolate mofetil (MMF) or cyclophosphamide (CYC) with steroids (e.g. methylprednisolone) for induction and then MMF and azathioprine for maintenance therapy.

For refractory LN (patients who fail treatment with either MMF or CYC), the recommendation is to switch treatments, either from MMF to CYC, or from CYC to MMF. Rituximab may also be given at this stage.^{11,13}

PLACE OF TECHNOLOGY

If licensed, belimumab will offer an additional treatment option for patients with LN who are uncontrolled on standard of care who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	BLISS-LN, NCT01639339, 114054, EudraCT 2011-004570-28; belimumab vs placebo both in addition to standard therapy; phase III
Sponsor	Human Genome Sciences Inc., a GSK Company
Status	Ongoing
Source of Information	Trial registry ^{1,15}
Location	EU (including the UK), USA, Canada and other countries
Design	Randomised, placebo-controlled, double-blind, parallel assignment
Participants	N=448; aged ≥18 years old; SLE, diagnosis by the American College of Rheumatology (ACR) criteria, active LN with a confirmed biopsy in past 6 months; requiring /receiving induction therapy with standard of care medications; anti-nuclear antibody-positive
Schedule	Randomised to belimumab plus standard therapy; belimumab 10mg/kg IV administered on days 0, 14, 28 and then every 28 days in 28 day cycles through week 100; or placebo plus standard therapy*; placebo IV administered on days 0, 14, 28 and then every 28 days in 28 day cycles through week 100.

	<p>Standard therapy*:</p> <ul style="list-style-type: none"> • High-dose steroids (for example, methylprednisolone) plus cyclophosphamide for induction therapy followed by azathioprine for maintenance therapy OR • High-dose steroids plus mycophenolate for induction therapy followed by mycophenolate for maintenance therapy <p>*Induction therapy starts before the first dose of study drug (belimumab or placebo). Maintenance therapy begins after completion of induction therapy and continues for the remainder of the study^c</p>
Follow-up	<p>Follow-up duration: 104 weeks (the controlled period of the study).</p> <p>Active treatment duration: 100 weeks. Participants on both arms of treatment who successfully complete the 104-week study can opt-in to participate in an open-label extension period. All participants will receive belimumab 10mg/kg IV every 28 days for an additional 6 months.</p>
Primary Outcomes	Number of participants with primary efficacy renal response at week 104 [Time frame: week 104]
Secondary Outcomes	<ul style="list-style-type: none"> • Number of participants with a complete renal response at week 104 [Time frame: week 104] • Number of participants with primary efficacy renal response at week 52 [Time frame: week 52] • Number of participants who experienced adverse events [Time frame: up to 136 weeks] • Time to death or renal-related event [Time frame: up to 104 week] • Number of participants with ordinal renal response at week 104 [Time frame: week 104]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	<p>Estimated study completion date reported as March 2020.</p> <p>The company anticipates publication of study in Q1 2020.^d</p>

ESTIMATED COST

Belimumab is already marketed in the UK. One vial of belimumab 120mg powder for concentrate for solution for infusion costs £121.50 and one vial of belimumab 400mg powder for concentrate for solution for infusion costs £405.00.¹⁶

^c Information provided by GlaxoSmithKline

^d Information provided by GlaxoSmithKline on UK PharmaScan

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Belimumab for treating active autoantibody-positive systemic lupus erythematosus (TA397). June 2016
- NICE evidence summary. Systemic lupus erythematosus: oral mycophenolate (ESUOM36). November 2014.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Rituximab for the treatment of Systemic Lupus Erythematosus in adults. A13/PS/a. August 2013

OTHER GUIDANCE

- British Society for Rheumatology. Guideline for the management of systemic lupus erythematosus in adults. 2017.¹¹
- Bertias GK, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. 2012.¹³
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ADDITIONAL INFORMATION

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