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HEALTH TECHNOLOGY BRIEFING
AUGUST 2021

Baricitinib for systemic lupus erythematosus

NIHRIO ID	12436	**NICE ID**	10332
Developer/Company	Eli Lilly and Company Limited	**UKPS ID**	654433

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Baricitinib is in clinical development for adults with Systemic Lupus Erythematosus (SLE). 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. Mild SLE can cause joint problems and tiredness, whereas severe cases can be life threatening. Currently, conventional SLE treatments, such as corticosteroids and immunosuppressants, are known to have issues with efficacy and long-term toxicity.

Baricitinib is an inhibitor of Janus kinase (JAKs) enzymes that mediate the pathways involved in the inflammatory process in SLE and other inflammatory diseases. Baricitinib is taken orally and is currently licensed for the treatment of moderate to severe active rheumatoid arthritis and atopic dermatitis in adult patients that have not responded well to other therapies. If licensed, baricitinib will offer an additional treatment option for adults with SLE.

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

Treatment for adult patients with systemic lupus erythematosus (SLE).[1]

TECHNOLOGY

DESCRIPTION

Baricitinib (Olumiant, LY3009104) is a Janus kinase (JAK) inhibitor. JAK inhibitors help disrupt how cells respond to some cytokines. Cytokines are proteins that allow cells to communicate with each other, and excess cytokines may cause inflammation.[2] Within the intracellular signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (JAK-STATs), which activate gene expression within the cell. Baricitinib modulates these signalling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs.[3] Dysregulation of the cytokines is a hallmark of SLE.[4]

Baricitinib is currently in phase III clinical development for treatment of adults (≥ 18 years old) with SLE (NCT03843125, NCT03616912, NCT03616964).[1,5,6] Patients are orally administered 2mg baricitinib or 4mg baricitinib.[7]

INNOVATION AND/OR ADVANTAGES

Patients with SLE have substantial unmet medical need.[7] In a phase II study, baricitinib 4 mg dose, but not the 2 mg dose, significantly improved the signs and symptoms of active SLE in patients who were not adequately controlled despite standard of care therapy, with a safety profile consistent with previous studies of baricitinib.[7,8]

In a double-blind, multicenter, randomized, placebo-controlled, 24-week phase 2 study across 11 countries, baricitinib treatment at a dose of 4 mg dose significantly improved the signs and symptoms of active SLE, with a high-resolution rate of 67% in SLEDAI-2K (measurement of disease activity) arthritis or rash.[9,10]

A recently published systematic review of interventions for cutaneous disease in SLE has found that the strength of the evidence underpinning the phase II (NCT02708095) results was low. Further phase III studies (NCT03616912, NCT03616964) are currently ongoing.[11]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Baricitinib is currently licenced in the UK for the treatment of:[3]

- Moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. It may be used as a monotherapy or in combination with methotrexate.
- Moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.

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The most commonly reported adverse events (≥ 10%) among patients receiving baricitinib are upper respiratory tract infections and hypercholesterolaemia.[3]

Baricitinib is in phase II clinical development for:[12]

- Autoinflammatory disorders
- Alopecia areata
- Aicardi Goutières Syndrome
- Polymyalgia rheumatic
- Idiopathic inflammatory myopathies.

Baricitinib is also in phase III clinical development for:[13]

- Paediatric atopic dermatitis
- Juvenile idiopathic arthritis
- Uveitis
- Alopecia areata
- Autoinflammatory disorders
- COVID

In June, 2018, the US Food and Drug Administration (FDA) approved a once-daily dose of 2 mg baricitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis.[14] The FDA has also granted baricitinib:

- Fast track designation, which is being studied for the treatment of SLE, on December 2018.[15]
- Emergency use authorization for the treatment of hospitalized patients with COVID-19 in November 2020.[16]

PATIENT GROUP

DISEASE BACKGROUND

Systemic lupus erythematosus (SLE) is a chronic, multi-organ autoimmune disease that can cause widespread tissue and organ damage.[15] 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.[17] SLE patients and lupus-like disease mouse models reveal many examples of genetic abnormalities that impact different self-tolerance checkpoints leading to overproduction of autoantibodies.

SLE is characterized by periods of flare and remission and is associated with a variety of symptoms, including extreme fatigue, unexplained fever, joint pain/swelling and butterfly rash.[15] Some patients experience periods where their disease flares up (relapses) and periods where their symptoms settle down (remission) whereas some patients do not notice any difference and symptoms are constant. Mild SLE causes joint and skin problems and tiredness. Moderate SLE causes inflammation of other parts of the skin and body, including the lungs, heart and kidneys. Severe SLE causes life-threatening involvement to the heart, lungs, brain,

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bone marrow or kidneys and are more likely to cause irreversible damage accrual in the first years of disease.[18]

The causes of SLE are unknown but are believed to be linked to environmental, genetic and hormonal factors.[19] Some of the environmental triggers linked to SLE include; excessive sun exposure, viruses and other infections, household chemicals and toxic exposures.[20] Normal variations (polymorphisms) in many genes can affect the risk of developing SLE and in most cases multiple genetic factors are thought to be involved. In rare cases, SLE is caused by mutations in single genes. Most of the genes associated with SLE are involved in immune system function and variations in these genes likely affect proper targeting and control of the immune response.[21]

CLINICAL NEED AND BURDEN OF DISEASE

SLE is a relatively uncommon disease. The prevalence has been estimated in several different countries mostly in the developed world, using different techniques of case ascertainment. Three English studies have produced prevalence estimates of: 12/100,000, 25/100,000 and 28/100,000.[22] A 2016 UK retrospective cohort study that used the Clinical Practise Research Datalink (CPRD) database to study the incidence and prevalence of SLE in the UK between 1999 and 2012, concluded that the incidence during the study period was 4.91/100 000 person-years (95% CI 4.73 to 5.09), with an annual 1.8% decline ($p<0.001$). In contrast, the prevalence increased from 64.99/100 000 in 1999 (95% CI 62.04 to 67.93) (0.065%) to 97.04/100 000 in 2012 (95% CI 94.18 to 99.90) (0.097%). SLE was six times more common in women. The peak age of incidence was 50-59 years.[23]

NHS England has previously reported that approximately 15,000 people in England and Wales live with SLE, predominantly women, with a peak incidence at the age of 25-30 years old. The incidence, prevalence and severity of SLE is higher in African-Caribbean, South Asian and Chinese populations compared to European whites. In these racial/ethnic groups there is a higher incidence of renal involvement, which is associated with a higher mortality rate and end-stage kidney disease may occur in up to 40% of cases.[24]

Approximately 20-30% of patients continue to have high disease activity despite standard therapies, or have major organ involvement particularly associated with a worse prognosis (e.g. renal, neuropsychiatric, haematological involvement). These groups require therapy with more potent immunosuppression such as IV cyclophosphamide or mycophenolate mofetil.[24]

A proportion of these patients will, however, continue to have active uncontrolled disease despite therapy, or will have unacceptable toxicities from such drugs. In others, disease control will require an unacceptably high dose of corticosteroids, which, in this population, is associated with the development of significant co-morbidities (irreversible organ damage) such as bone, cardiovascular, neuropsychiatric and metabolic consequences. These refractory patients (<10% of all cases of SLE) require access to treatment with a biologic drug such as rituximab.[24]

In England, in 2019-2020, there were 6,644 finished consultant episodes (FCE) for SLE (ICD-10 code M32) which resulted in 5,982 admissions and 7,584 FCE bed days.[25] Death from active SLE is rare in the UK. However, 10% mortality over 20 years with a mean age of death of 53.7 years has been reported.[26]

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PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Currently there is no cure for SLE but there are a series of general measures, that include sun protection, avoid smoking and controlling obesity, hypertension and other co-morbidities. The medications available can help relieve the symptoms and try to reduce the chances of organ damage.[27,28] The drugs used to treat SLE will depend on the severity of disease and which parts of the body are affected, but their use may be limited due to adverse events and comorbidities.[29]

CURRENT TREATMENT OPTIONS

Belimumab is recommended by NICE as an add-on treatment for active autoantibody-positive SLE in adults only if all of the following apply:[30]

- There is evidence for serological disease activity (defined as positive anti-double-stranded DNA and low complement) and a SELENA-SLEDAI score of greater than or equal to 10 despite standard treatment.
- Treatment with belimumab is continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more.

Patients who experience joint or muscle pain as a result of SLE are often prescribed anti-inflammatory, immunomodulatory and immunosuppressive drugs by physicians to ease symptoms including:[27,31]

- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen and diclofenac
- Corticosteroids such as prednisolone[32]
- Hydroxychloroquine sulphate[33]
- Immunosuppressants such as azathioprine,[34] methotrexate, mycophenolate mofetil (MMF), tacrolimus and cyclophosphamide

PLACE OF TECHNOLOGY

If licenced, baricitinib will offer an additional treatment option for adults with systemic lupus erythematosus (SLE).

CLINICAL TRIAL INFORMATION

Trial	**SLE-BRAVE-X; NCT03616964; 2017-005028-11**; A Phase 3, Double-Blind, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients With Systemic Lupus Erythematosus (SLE) **Phase III–** Recruiting **Location(s): 14 EU countries, UK, and US, and other countries.** **Primary completion date**: **April 2025**

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Trial design	Randomized, double-blind, multicenter, double masking, parallel assignment.
Population	N = 1,100 (planned), patients aged 18 years or older, patients that have completed the final treatment study visit of an originating study, such as study JAHZ (NCT03616912) or Study JAIA (NCT03616964).
Intervention(s)	- Baricitinib 4mg administered orally for 156 weeks. - Baricitinib 2mg administered orally for 156 weeks.
Comparator(s)	No comparator
Outcome(s)	Primary outcome(s); - Percentage of Participants with Treatment-Emergent Adverse Events (TEAEs) [Time Frame: Baseline through Week 156] - Percentage of Participants with Adverse Events of Special Interest (AESIs) [Time Frame: Baseline through Week 156] - Percentage of Participants with Serious Adverse Events (SAEs) [Time Frame: Baseline through Week 156] - Percentage of Participants with Temporary Investigational Product Interruptions [Time Frame: Baseline through Week 156] - Percentage of participants with temporary investigational product interruptions - Percentage of Participants with Permanent Investigational Product Discontinuations [Time Frame: Baseline through Week 156] - Percentage of participants with permanent investigational product discontinuations See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**BRAVE I; NCT03616912; 2017-005026-37;** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of Baricitinib in Patients With Systemic Lupus Erythematosus **Phase III-** Active, not recruiting **Location(s):** 8 EU countries, UK, US, and other countries **Primary completion date:** May 2022
Trial design	Randomized, double-blind, placebo controlled, parallel group, double masking.
Population	N = 809 (planned), patients aged 18 years or older, patients with a clinical diagnosis of SLE at least 24 weeks prior to screening.
Intervention(s)	- Baricitinib 4mg administered orally for 52 weeks.

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	- Baricitinib 2mg administered orally for 52 weeks.
Comparator(s)	Placebo administered orally for 52 weeks.
Outcome(s)	Primary outcome(s); Percentage of Participants Achieving a Systemic Lupus Erythematosus Responder Index 4 (SRI-4) Response (High Dose) [Time Frame: Week 52] - Percentage of participants achieving SRI-4 response (high dose). See trial record for full list of other outcomes
-	-
Results (safety)	-

Trial	**BRAVE II; NCT03616964;** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of Baricitinib in Patients With Systemic Lupus Erythematosus **Phase III**- Active, not recruiting **Location(s):** 6 EU countries, US, and other countries **Primary completion date:** October 2021
Trial design	Randomized, parallel assignment, double masking, double-blind, placebo controlled.
Population	N = 750 (planned), patients aged 18 years or older, patients with a clinical diagnosis of SLE at least 24 weeks prior to screening.
Intervention(s)	- 2mg baricitinib administered orally for 52 weeks. - 4mg baricitinib administered orally for 52 weeks.
Comparator(s)	Placebo administered orally for 52 weeks.
Outcome(s)	Primary outcome: - Percentage of Participants Achieving a Systemic Lupus Erythematosus Responder Index 4 (SRI-4) Response (High Dose) [Time Frame: Week 52] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**NCT02708095;** A Randomized, Double-Blind, Placebo-Controlled, Parallel- Group, Phase 2 Study of Baricitinib in Patients With Systemic Lupus Erythematosus (SLE) **Phase II** - Completed **Location(s):** 5 EU countries, US, and other countries **Study completion date:** October 2017
Trial design	Randomized, double-blind, placebo controlled, parallel-group, double masking.
Population	N = 314 (actual), patients aged 18 years or older, patients that have received a diagnosis of SLE at least 24 weeks prior to

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	screening, meeting the American College of Rheumatology (ACR) 1982 revised criteria OR the 2012 Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) criteria.
Intervention(s)	- Participants received 2 (milligrams) mg of Baricitinib tablet orally once a day for 24 weeks. - Participants received 4 mg of Baricitinib tablet orally once a day for 24 weeks.
Comparator(s)	Participants received Placebo orally once daily (QD) for 24 weeks.
Outcome(s)	Primary Outcome: Proportion of Participants who Achieve Remission of Arthritis and/or Rash defined by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) [Time Frame: Week 24] See trial record for full list of other outcomes
Results (efficacy)	At week 24, resolution of SLEDAI-2K arthritis or rash was achieved by 70 (67%) of 104 patients receiving baricitinib 4 mg (odds ratio [OR] vs placebo 1·8, 95% CI 1·0-3·3; p=0·0414) and 61 (58%) of 105 patients receiving baricitinib 2 mg (OR 1·3, 0·7-2·3; p=0·39).[7]
Results (safety)	Adverse events were reported in 68 (65%) patients in the placebo group, 75 (71%) patients in the baricitinib 2 mg group, and 76 (73%) patients in the baricitinib 4 mg group. Serious adverse events were reported in ten (10%) patients receiving baricitinib 4 mg, 11 (10%) receiving baricitinib 2 mg, and five (5%) receiving placebo; no deaths were reported. Serious infections were reported in six (6%) patients with baricitinib 4 mg, two (2%) with baricitinib 2 mg, and one (1%) with placebo.[7]

ESTIMATED COST

Cost of baricitinib was confidential at the time of producing this briefing.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance – proposed. Anifrolumab for treating active autoantibody-positive systemic lupus erythematosus (GID-TA10676). Expected publication date: April 2022.
- NICE technology appraisal guidance in development. Belimumab for treating active autoantibody-positive systemic lupus erythematosus (Review of TA397) (GID-TA10626). Expected publication date: November 2021.

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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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