# Health Technology Briefing
# October 2023

# Obinutuzumab with mycophenolate mofetil for treating lupus nephritis

| Company/Developer | Roche Products Ltd |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 11864 | NICE ID: Not available | UKPS ID: 663137 |
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## Licensing and Market Availability Plans

Currently in phase III clinical trials

## Summary

Obinutuzumab in combination with mycophenolate mofetil is in clinical development for the treatment of class III or class IV lupus nephritis (LN) in adults. LN is a manifestation of a disease called systemic lupus erythematosus (SLE). In LN, the immune system (the body's natural defences) attacks the kidneys, causing inflammation and kidney damage. LN remains a substantial cause of morbidity and mortality in lupus patients. Treatment of LN has been challenged by the limited number of effective medicinal products and side-effects associated with them.

Obinutuzumab is a monoclonal antibody, a type of protein that has been designed to recognise and attach to a specific structure (called an antigen) that is found on certain cells in the body. Obinutuzumab has been designed to attach to a protein called CD20, which is present on the surface of all B cells (B cells are recognised as key mediators of how SLE develops). As a result, it causes B cell depletion in patients with LN thereby making it an effective choice in the management of LN. Obinutuzumab is administered as an intravenous infusion. If licensed, obinutuzumab in combination with mycophenolate mofetil will provide an additional treatment option for LN in adults who currently have few well-tolerated and effective treatment options.

## Proposed Indication

Treatment of class III or class IV lupus nephritis (LN) in adults.[1]

## Technology

### Description

Obinutuzumab (Gazyvaro) is a recombinant monoclonal humanised and glycoengineered type II anti-CD20 antibody of the IgG1 isotype.[2] Obinutuzumab is designed to attach to CD20, a protein found only on certain types of B-cells. It is thought to work by attacking targeted cells both directly, and together with the body's immune system.[3] Obinutuzumab displays efficient antibody-dependent cellular cytotoxicity due to its greater affinity for the FcγRIII (a systemic lupus erythematosus susceptibility gene) on effector cells.[4] As a result, it causes B cell depletion in patients with LN.[5]

Obinutuzumab in combination with mycophenolate mofetil is currently in clinical development for the treatment of class III or class IV lupus nephritis in people aged 18 to 75 years. In the phase III REGENCY study (NCT04221477), patients receive obinutuzumab by IV infusion at a dose of 1000 mg at baseline and weeks 2, 24, 26, 50 and 52 plus mycophenolate mofetil and oral prednisone, and subsequently from week 80 and every 6 months thereafter, based on adequate response at week 76.[1]

### Key Innovation

Previous studies of two type I anti-CD20 antibodies (rituximab and ocrelizumab) did not show improved rates of complete renal response when added to standard therapy in patients with LN.[6] As rituximab is a chimeric antibody, some rituximab-treated patients who initially respond well develop neutralizing antibodies with repeat cycles on treatment. Obinutuzumab may be the most promising anti-CD20 therapy for SLE. This may be because while all of the next generation CD20 therapies are humanized or fully human, obinutuzumab is a type-2 CD20 antibody that is glycoengineered to have a stronger interaction with Fc gamma receptors and a stronger resistance to internalization than rituximab.[7] LN remains a substantial cause of morbidity and mortality in lupus patients. Current therapies retain a significant unmet medical need regarding rates of complete response, preventing relapse of lupus nephritis, progression of chronic kidney disease to kidney failure, drug toxicity, and pill burden-related drug non-adherence.[4]

Treatment of LN has been challenged by the limited number of effective medicinal products and side-effects associated with them. If licensed, obinutuzumab in combination with mycophenolate mofetil will provide an additional treatment option for patients with LN who currently have few well-tolerated and effective treatment options.

### Regulatory & Development Status

Obinutuzumab in combination with mycophenolate mofetil does not currently have Marketing Authorisation in the EU/UK for any indication.

In the EU/UK, obinutuzumab in combination has Marketing Authorisation for the following:[2]

- In combination with chlorambucil for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia and with comorbidities making them unsuitable for full-dose fludarabine based therapy.
- In combination with chemotherapy, followed by obinutuzumab maintenance therapy for the treatment of patients with previously untreated advanced follicular lymphoma.

- In combination with bendamustine followed by obinutuzumab maintenance for the treatment of patients with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

Obinutuzumab in combination with mycophenolate mofetil is also in phase III development for systemic lupus erythematosus (SLE) and childhood nephrotic syndrome.[8]

Obinutuzumab was granted a Breakthrough Therapy designation by the US FDA in September 2019 for adults with lupus nephritis.[9]

## Patient Group

### Disease Area and Clinical Need

Lupus nephritis (LN) is a type of kidney disease caused by SLE. Lupus is an autoimmune disease, a disorder in which the body's immune system attacks the body's own cells and organs.[10] Inflammation of the kidneys can harm the ability of the overall renal system to properly remove waste from blood, maintain the correct amount of body fluids, and regulate hormone levels for controlling blood pressure and blood volume.[11] Class III LN is used for focal glomerulonephritis (involving <50% of total number of glomeruli) and class IV for diffuse glomerulonephritis (involving ≥50% of total number of glomeruli).[12] The symptoms of LN include; foamy urine, oedema (in the legs, feet, ankles, hands or face), high blood pressure, joint pain or swelling, muscle pain, fever with no known cause and a red rash often on the face or across the nose and cheeks.[10]

There are currently around 60,000 people with SLE in England and Wales and around 3,000 people are diagnosed with SLE each year. Around 40% to 60% of people with SLE develop lupus nephritis. Compared with people who are described as white, the prevalence of lupus nephritis is around 4, 18 and 19 times higher, respectively, among those with Indo-Asian, Afro-Caribbean, and Chinese family backgrounds. Lupus nephritis is more prevalent in women than in men.[13] In England 2021-22, there were 2,873 finished consultant episodes (FCE) and 2,496 admissions for SLE with organ or system involvement (ICD-10 code M32.1) which resulted in 3,990 FCE bed days and 2,004 day cases.[14]

### Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends voclosporin with mycophenolate mofetil for treating LN.[15] In the UK, belimumab is recommended under expert supervision for treating lupus nephritis.[16]

## Clinical Trial Information

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| Trial | NCT02550652, EudraCT 2015-002022-39; A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Obinutuzumab in Patients With ISN/RPS 2003 Class III or IV Lupus Nephritis<br>**Phase II** – Active, not recruiting<br>**Locations**: 3 EU countries, USA, and other countries<br>**Primary completion date**: January 2019 |
| Trial Design | Randomised, parallel assignment, double-blind |

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| Population | N=126 (actual); subjects with class III or IV Lupus Nephritis (LN) aged 18 to 75 years old |
| Intervention(s) | • Obinutuzumab 1000mg (IV)<br>• Mycophenolate mofetil/mycophenolic acid (oral)<br>• Methylprednisolone (IV)<br>• Prednisone (oral) |
| Comparator(s) | • Matched placebo<br>• Mycophenolate mofetil/mycophenolic acid (oral)<br>• Methylprednisolone (IV)<br>• Prednisone (oral) |
| Outcome(s) | Primary outcome: Percentage of participants who achieve protocol defined complete renal response (CRR) at week 52 (Time Frame: from baseline to week 52)<br><br>See trial record for full list of other outcomes |
| Results (efficacy) | A total of 125 patients were randomised and received blinded infusions. Achievement of CRR was greater with obinutuzumab at week 52 (primary endpoint, 22 (35%) vs 14 (23%) with placebo; percentage difference, 12% (95% CI −3.4% to 28%), p=0.115) and at week 104 (26 (41%) vs 14 (23%); percentage difference, 19% (95% CI 2.7% to 35%), p=0.026). Improvements in other renal response measures, serologies, estimated glomerular filtration rate and proteinuria were greater with obinutuzumab.[17] |
| Results (safety) | Obinutuzumab was not associated with increases in serious adverse events, serious infections or deaths. Non-serious infusion-related reactions occurred more frequently with obinutuzumab.[17] |

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| Trial | **REGENCY,** NCT04221477, EudraCT 2019-004034-42; A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety Of Obinutuzumab In Patients With ISN/RPS 2003 Class III Or IV Lupus Nephritis<br>**Phase III** – Active, not recruiting<br>**Locations**- 5 EU countries, UK, USA, Canada, and other countries<br>**Primary completion date**: August 2024 |
| Trial Design | Randomised, parallel-assignment, double-blind |
| Population | N=252 (planned); Subjects with active or active/chronic ISN/RPS 2003 Class III or IV proliferative lupus nephritis aged 18 to 75 years |
| Intervention(s) | • Obinutuzumab 1000mg (IV)<br>• Mycophenolate mofetil (oral)<br>• Prednisone (oral)<br>• Methylprednisolone 80mg (IV)<br>• Acetaminophen (oral)<br>• Diphenhydramine 50mg (oral) |

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| Comparator(s) | • Matched placebo<br>• Mycophenolate mofetil (oral)<br>• Prednisone (oral)<br>• Methylprednisolone 80mg (IV)<br>• Acetaminophen (oral)<br>• Diphenhydramine 50mg (oral) |
| Outcome(s) | Primary outcome: Percentage of participants with CRR (Time frame: at week 76)<br><br>See trial record for full list of other outcomes |
| Results (efficacy) | - |
| Results (safety) | - |

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| Trial | **OBILUP**, NCT04702256; Induction Therapy for Lupus Nephritis With no Added Oral Steroids: An Open Label Randomised Multicentre Controlled Trial Comparing Oral Corticosteroids Plus Mycophenolate Mofetil (MMF) Versus Obinutuzumab and MMF<br>**Phase III** - Recruiting<br>**Location**: France<br>**Primary completion date**: December 2031 |
| Trial Design | Randomised, parallel-assignment, open-label |
| Population | N=196 (planned); subjects with class III or IV lupus nephritis with active lesions in at least 10% of the viable glomeruli aged 14 years and older |
| Intervention(s) | Obinutuzumab (IV) plus mycophenolate mofetil (oral)<br>Methylprednisolone, paracetamol and dexchlorpheniramine. |
| Comparator(s) | Methylprednisolone plus prednisone plus MMF |
| Outcome(s) | Primary outcomes:<br>• CRR [Time frame: at week 52]<br>• Proteinuria measurement (Time frame: at baseline and week 52)<br>See trial record for full list of other outcomes |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

The NHS indicative cost of one vial of obinutuzumab (1000mg/40ml) is £3,312.00.[18]

## Relevant Guidance

NICE Guidance

- NICE technology appraisal. Voclosporin with mycophenolate mofetil for treating lupus nephritis (TA882). May 2023.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Rituximab for refractory Systemic Lupus Erythematosus (SLE) in adults and post-pubescent children. 200402P. July 2020.
- NHS England. Interim Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults. A13/PS/a. August 2013.

Other Guidance

- Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis. 2019.[19]
- British Society for Rheumatology. Guideline for the management of systemic lupus erythematosus in adults. 2017.[20]
- Bertsias 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.[21]

## Additional Information

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