Medicinrådet

Bilag til Medicinrådets vurdering af obinutuzumab til behandling af voksne med aktiv lupus nefritis i klasse III eller IV med eller uden samtidig klasse V

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. obinutuzumab
2. Forhandlingsnotat fra Amgros vedr. obinutuzumab
3. Ansøgers endelige ansøgning vedr. obinutuzumab

Høringssvar fra Roche Pharmaceuticals A/S angående Medicinrådets anbefaling vedrørende obinutuzumab til behandling af lupus nephritis i klasse III eller IV, med eller uden samtidig klasse V.

Roche takker for det fremsendte udkast til Medicinrådets vurderingsrapport og ønsker at kommentere på et centralt element af den sundhedsøkonomiske vurdering.

Roche mener, at Medicinrådets antagelser i sin hovedanalyse vedrørende varighed af effekt efter afsluttet behandling med obinutuzumab bør ses som det absolut mest pessimistiske scenarie i Rådets beslutningsgrundlag. I vurderingsrapporten beskrives det at man for antagelsen om varighed af respons på obinutuzumab har taget udgangspunkt i NOBILITY, hvor patienter fortsat havde respons i uge 104 efter at have modtaget behandling i uge 2, 24 og 26. På baggrund af dette har Medicinrådet antaget, at patienter har effekt af obinutuzumab i 76 uger efter endt behandling, hvorefter at effekt vil begynde at aftage over 2 år, således at al effekt af obinutuzumab er helt forsvundet for samtlige patienter 3,5 år efter endt behandling. En sådan antagelse vil kun være meningsfuld, såfremt det forventes at alle patienter i NOBILITY har mistet effekt af obinutuzumab 2 år efter studiets afslutning. Dette er der ikke nogen indikation af skulle være tilfældet ud fra tilgængeligt data fra studiet (1). Roche har forståelse for at Medicinrådet er nødt til at adressere usikkerheder om varighed af effekt, men mener at en sådan antagelse er for konservativ og opfordrer derfor Medicinrådet til at lægge stor vægt på følsomhedsanalyserne, hvor der anvendes en længere varighed af respons på obinutuzumab relativt til hovedanalysen. Ligeledes opfordrer Roche til at man ikke lægger vægt på de følsomhedsanalyser, hvor der anvendes endnu mere pessimistiske antagelser om varighed af effekt end den der kan findes i hovedanalysen. Roche finder disse analyser ubegrundede jf. resultaterne af REGENCY og NOBILITY.

Roche håber, at Medicinrådet vil tage disse overvejelser med i deres endelige beslutning.

Med Venlig Hilsen

Roche Pharmaceuticals A/S

1. Furie RA, Aroca G, Cascino MD, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. Annals of the Rheumatic Diseases 2022;81:100-107.

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28.05.2026

KLE/LSC

Forhandlingsnotat

Dato for vurdering i Medicinrådet	24.06.2026
Leverandør	Roche
Lægemiddel	Gazyvaro (obinutuzumab)
Ansøgt indikation	Gazyvaro i kombination med mycophenolatmofetil (MMF) til behandling af voksne patienter med aktiv lupus nefritis (LN) i klasse III eller IV med eller uden samtidig klasse V.
Nyt lægemiddel /Indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Gazyvaro:

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP (DKK)	Nuværende rabat ift. AIP	Ny SAIP pr. 01.11.2026 (DKK)	Rabat ift. AIP pr. 01.11.2026
Gazyvaro	1.000 mg (1 stk.)	22.264,71	[redacted]	[redacted]	[redacted]	[redacted]

Aftaleforhold

Amgros har en eksisterende aftale på Gazyvaro. Aftalen gælder til den 31.10.2026. Der har netop været udbud på lægemidlet med aftalestart 01.11.2026.

[redacted]

Konkurrencesituationen

Den nuværende standardbehandling til lupus nefritis er cyclophosphamid eller mycophenolatmofetil (MMF) begge i kombination med prednisiolon. Alle patienter gives desuden hydroxychloroquin som basisbehandling efter at induktionsbehandlingen er opstartet. Gazyvaro gives som tillæg til standardbehandlingen med MMF i kombination med glukokortikoid og doseringen af standardbehandlingen er den samme, uanset om det gives alene eller som tillæg til Gazyvaro, hvorfor de ikke er inkluderet i beregningen i tabel 2.

Medicinrådet vurderer, at man vil seponere behandlingen efter doseringen i uge 52, dvs. efter den første vedligeholdelsesbehandling, fordi der på nuværende tidspunkt ikke er publiceret data for behandlingens effekt ved behandling udover 52 uger. Behandling med MMF, glukokortikoid og hydroxychloroquin fortsættes som vedligeholdelsesbehandling.

Tabel 2 viser lægemiddeludgifter ved behandling med Gazyvaro for et behandlingsforløb på fem doseringer (fire doseringer i opstartsperioden samt en dosering 6 måneder efter opstartsperioden).

Tabel 2: Lægemiddeludgifter pr. patient for et behandlingsforløb på fem dosseringer.

Lægemiddel	Styrke (pakning)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsforløb (SAIP, DKK)
Gazyvaro	1.000 mg (1 stk.)	Initialt: 1.000 mg, i.v. Uge 2: 1.000 mg, i.v. Uge 24: 1.000 mg, i.v. Uge 26: 1.000 mg, i.v. Uge 52: 1.000 mg, i.v	[redacted]	[redacted]

*Jf. Medicinrådets udkast til vurderingsrapport.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke ansøgt	
Sverige	Ikke ansøgt	
England	Anbefalet	Link til anbefaling

Opsummering

Amgros har en aftale på Gazyvaro frem til 31.10.2027. Leverandøren kan først tilbyde en ny pris efter denne dato.

Application for the assessment of obinutuzumab (Gazyvaro) for treatment of adult patients with active Class III or IV with or without concomitant Class V lupus nephritis (LN)

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

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Abbreviations

AD	Active disease
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CCOD	Clinical cut-off date
CDC	Complement-dependent cytotoxicity
CEM	Cost effectiveness model
CI	Confidence interval

CR	Complete response
CYC	Cyclophosphamide
CKD	Chronic kidney disease
CRR	Complete renal response
DCD	Direct cell death
DMC	Danish Medicines Council
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQol 5-Dimension 5-Level questionnaire
ESKD	End-stage kidney disease
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUVs	Health state utility values
IRR	Infusion-related reaction
ISN/RPS	International Society of Nephrology/Renal Pathology Society
IV	Intravenous
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
LN	Lupus nephritis
LY	Life-year
MMF	Mycophenolate mofetil
MMRM	Mixed-effect model of repeated measures
MPD	Methylprednisone
MPDL	Methylprednisolone
Msm	Multi state model
N/A	Not available
NE	Not estimable
NPR	National Patient Registry
N/R	Not relevant
Obi	Obinutuzumab
ORR	Overall renal response
PDS	Prednisone
PR	Partial response
PRR	Partial renal response
PSA	Probabilistic sensitivity analysis
PT	Preferred term
QALY	Quality-adjusted life year
QoL	Quality of life
SAE	Serious adverse event
SDI	Short duration infusion
SE	Standard Error
SLE	Systemic lupus erythematosus
SLR	Systematic literature review
SOC	System organ class
TP	Transition probability

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Gazyvaro
Generic name	Obinutuzumab
Therapeutic indication as defined by EMA	Gazyvaro in combination with mycophenolate mofetil (MMF) is indicated for the treatment of adult patients with active Class III or IV, with or without concomitant Class V, lupus nephritis (LN).
Marketing authorization holder in Denmark	Roche Pharmaceuticals A/S
ATC code	L01FA03
Combination therapy and/or co-medication	Mycophenolate mofetil (MMF) and glucocorticoids
Date of EC approval	December 4, 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes (May 21, 2014)
Other therapeutic indications approved by EMA	**Chronic lymphocytic leukaemia (CLL)** Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy. **Follicular lymphoma (FL)** Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced FL. Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. See section 5.1 in the EMA SmPC for reference.

Overview of the medicine	
Other indications that have been evaluated by the DMC (yes/no)	Yes, the following indication in FL has been evaluated by the DMC: Obinutuzumab in combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced FL
Joint Nordic assessment (JNHB)	Current treatment practices are similar across the Nordic countries (DK, FI, IS, NO, SE), however the product is not suitable for a joint Nordics assessment due to differences in reimbursement requirements.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	One package contains one vial of 40 mL concentrate, which contains 1000 mg obinutuzumab, corresponding to a concentrate before dilution of 25 mg/mL

2. Summary table

Summary	
Indication relevant for the assessment	Gazyvaro in combination with mycophenolate mofetil (MMF) is indicated for the treatment of adult patients with active Class III or IV, with or without concomitant Class V, lupus nephritis (LN).
Dosage regiment and administration	Recommended obinutuzumab dosing is 1000 mg IV on Day 1, Day 15, and Weeks 24, 26, and 52, followed by 1000 mg (or 2x1000 mg) every 6 months thereafter.
Choice of comparator	Placebo plus MMF and glucocorticoids (e.g., prednisone) was chosen as the comparator because MMF-based regimens are the standard of care for class III/IV lupus nephritis under Danish guidelines, which consider MMF and cyclophosphamide equivalent. This choice aligns Danish clinical practice with the REGENCY trial (NCT04221477), where all patients received MMF and prednisone as standard therapy.
Prognosis with current treatment (comparator)	LN is a chronic condition that requires long-term immunosuppression. The aim of current treatment is to maintain kidney function, reduce disease activity and prevent flares. LN is a significant cause of morbidity and mortality. Despite current standard-of-care therapies (induction and maintenance with immunosuppressants and corticosteroids), the prognosis remains challenging: A significant proportion of patients progress to end-stage kidney disease (ESKD), with estimates of 10–30% within 15 years according to Danish guidelines. Historically, 6–19% develop ESKD after 10 years.

Summary	
	Mortality rates are significantly higher than the general population. A Danish nationwide cohort study observed a >10 fold increased risk of death in LN patients compared to the background population during the first 5 years post-diagnosis. Death directly attributable to kidney disease occurs in 5–25% of patients with proliferative LN within 5 years. Current therapies are limited by modest efficacy (only 20–30% achieve complete renal response (CRR) after 6 months) and high relapse rates (40–50%). Furthermore, long-term glucocorticoid use is associated with significant adverse effects and toxicity.
Type of evidence for the clinical evaluation	Head-to-head study
Most important efficacy endpoints (Difference/gain compared to comparator)	**Complete renal response (CRR) at Week 76 (primary endpoint):** Result: 46.4% for obinutuzumab vs. 33.1% for placebo; 13.4% adjusted difference (95% CI: 1.95, 24.84; p = 0.0232). **CRR with successful prednisone taper at Week 76 (key secondary):** Result: 42.7% for obinutuzumab vs. 30.9% for placebo; 11.9% adjusted difference (95% CI: 0.57, 23.18; p = 0.0421). **Proteinuric response at Week 76 (key secondary):** Result: 55.5% for obinutuzumab vs. 41.9% for placebo; 13.7% adjusted difference (95% CI: 2.01, 25.36; p = 0.0227). **Death or renal-related events through Week 76 (key secondary):** Result: 18.9% for obinutuzumab vs. 35.6% for placebo; -16.8% adjusted difference (95% CI: -27.50, -6.23; nominal p = 0.0026).
Most important serious adverse events for the intervention and comparator	**Serious adverse events (SAEs):** 32.4% for obinutuzumab vs. 18.2% for placebo. **Serious infections:** 13.2% for obinutuzumab vs. 6.1% for placebo. **COVID-19 pneumonia**: 5.1% for obinutuzumab vs. 0% for Placebo. **Fatal adverse events (AEs):** 2.2% for obinutuzumab vs. 1.5% for placebo
Impact on health-related quality of life	**Clinical documentation: EQ-5D-5L** *EQ-5D-5L utility index score:* Mean (SE) at baseline: [redacted]

Summary	
	Difference in mean (SE) at Week 76: [redacted] *EQ-5D-5L Visual Analog Scale (VAS):* Mean (SE) at baseline: [redacted] Difference in mean (SE) at Week 76: [redacted]) **Health economic model:** Health State Utility Values (HSUVs) were derived from REGENCY data using Danish weights where possible. For clinical states not captured within the REGENCY study, external data sources were utilized.
Type of economic analysis that is submitted	Cost-utility analysis (Markov Model)
Data sources used to model the clinical effects	REGENCY in initial states of the model (CKD 1-3b) along with external literature for health states representing more advanced disease (CKD 4-5)
Data sources used to model the health-related quality of life	REGENCY in initial health states of the model (CKD 1-3b) along with external literature for health states representing more advanced disease (CKD 4-5)
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	Treatment length and waning effect
Number of eligible patients in Denmark	If obinutuzumab is recommended 26 patients are expected to initiate treatment annually
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator and relevant outcomes

3.1 The medical condition

Lupus nephritis (LN) is a severe kidney manifestation of Systemic Lupus Erythematosus (SLE), a chronic autoimmune disease. It is characterized by immune dysregulation leading to inflammation and damage in the kidneys.

Pathophysiology

SLE is driven by genetic and environmental factors that result in immune dysregulation and a loss of self-tolerance (1, 2). This leads to B-cell driven autoantibody production and the deposition of immune complexes, causing systemic inflammation that affects multiple organs, including the kidneys (3, 4). In LN, B cells contribute to the disease by producing immunomodulatory cytokines and pathogenic antibodies, and by presenting antigens to T cells (5-7). This promotes the deposition of immune complexes within the glomeruli and tubulointerstitium of the kidney, resulting in inflammation and fibrosis (6, 7). These immune complexes can either be deposited from circulation or form *in situ* when autoantibodies target glomerular antigens or if apoptotic debris is not cleared (3). Their accumulation activates complement, recruits immune cells, and increases pro-inflammatory cytokine production, which can cause podocyte and glomerular capillary damage (1), ultimately leading to irreversible kidney failure (7).

Clinical presentation and symptoms

Symptoms of LN can vary, but most patients experience mild proteinuria and/or haematuria, and in some cases leukocyturia (1). Renal flares, defined as periods of increased disease activity requiring alternative or more intensive therapy, are a characteristic feature of LN (8). These flares lead to irreversible nephron loss and are characterized by increases in proteinuria, haematuria, and reduced kidney function (1, 9). Some patients may have 'silent' LN with normal urinalysis and renal function, and no proteinuria, where substantial renal involvement is only identified through kidney biopsy. Conversely, other patients may present with severe proteinuria, nephrotic syndrome, acute nephritic syndrome, or progressive renal failure (1, 10, 11). Shortness of breath, swollen joints, sleep disturbance, fatigue, and joint pain are among the most severe and bothersome symptoms reported by patients with LN (12). Fatigue, in particular, is associated with worse health-related quality of life and increased treatment dissatisfaction (13).

Patient prognosis with current treatment options

LN is a significant cause of morbidity and mortality in SLE patients. Historically, 6–19% of patients with LN develop End-Stage Kidney Disease (ESKD) after 10 years, necessitating dialysis or transplant (1, 14, 15), due to nephron loss from damaging flares. Death directly attributable to kidney disease occurs in 5–25% of patients with proliferative LN (Class III or IV, with or without Class V) within 5 years of onset (3). Overall survival at 10 years for LN patients is approximately 88% (16, 17), though it is significantly lower than for SLE patients without renal involvement (16, 18-21). A single renal flare can reduce the glomerular filtration rate by approximately 40% and usually results in irreversible nephron loss, shortening kidney lifespan (1). Patients with a low nephron number at birth or who have had previous nephron loss are at increased risk of developing ESKD (1).

The standard-of-care therapy for LN has typically involved glucocorticoids in combination with immunosuppressants like mycophenolate mofetil (MMF) or cyclophosphamide (CYC) (22, 23). However, these treatments have limitations, including modest efficacy (only 20–30% achieve complete renal response (CRR) after 6 months) (24, 25) and high relapse rates (40–50% during follow-up) (26, 27). Long-term glucocorticoid use is also associated with significant adverse effects such as infections, cardiovascular events, and osteoporosis (23, 28-32). Recently approved targeted therapies, belimumab and voclosporin, have increased the proportion of patients achieving a renal response compared to standard-of-care alone (43% vs 32% for belimumab; 41% vs 23% for voclosporin) (33-40). However, some patients still have active disease and remain at risk of ESKD and mortality (33, 34, 36-40). These newer treatments also have associated adverse effects (e.g., nephrotoxicity, neurotoxicity, hyperkalaemia with voclosporin, and infections/hypersensitivity with belimumab) (41-44) and treatment burden (e.g., frequent administration or high pill burden) (1-4, 33, 34, 37, 38) which can contribute to non-adherence (33-35, 45, 46). There is also heterogeneity in how renal response outcomes are defined across trials, complicating cross-treatment comparisons (39, 40, 47).

Disease influence on health-related quality of life

LN significantly impacts patients' and caregivers' daily lives, personal relationships, emotional well-being, overall quality of life (QoL), work productivity, and career, leading to increased indirect costs (48, 49). It is associated with considerable humanistic burden and reduced health-related quality of life (HRQoL) across multiple domains, including physical, emotional, social functioning, and general health (13, 22, 23, 50, 51). HRQoL is worse in patients with LN Class III or IV compared with Class I/II (13) and in patients with active LN compared to without active LN (13, 51).

3.2 Patient population

Hermansen et al. (2016) (52) assessed the incidence and prevalence of SLE and LN (all classes) in Denmark using data from the Danish National Patient Registry (NPR), identifying 1,644 incident cases of SLE (including 233 LN cases) between 1995–2011. The overall annual incidence rate per 100,000 for SLE was 2.35 (95% CI 2.24–2.49); specifically 0.69 (95% CI 0.60–0.78) for men and 3.96 (95% CI 3.75–4.17) for women. For

LN, the mean annual incidence rate per 100,000 was estimated to be 0.45 (95% CI 0.38–0.53); specifically 0.20 (95% CI 0.13–0.28) for men and 0.69 (95% CI 0.57–0.83) for women.

As of December 31, 2011, the overall point prevalence per 100,000 was 45.2 (95% CI 43.3–47.4) for SLE and 6.4 (95% CI 5.7–7.2) for LN. Sex-specific prevalence for SLE was 79.6 (95% CI 75.9–83.5) for women and 10.1 (95% CI 8.8–11.5) for men. For LN, the point prevalence was 10.6 (95% CI 9.2–12.1) for women and 2.1 (95% CI 1.6–2.9) for men. No newer data is available on the prevalence and incidence of LN in Denmark.

For the calculations, incidence rate and prevalence, values for 2011 were used together with population data from Statistics Denmark (53).

Table 1 Incidence and prevalence in the past 5 years (52)

Year	2021	2022	2023	2024	2025
Incidence in Denmark	26	26	27	27	27
Prevalence in Denmark	374	376	380	382	384
Global prevalence *	NR	NR	NR	NR	NR

* For small patient groups, also describe the worldwide prevalence.

To calculate patients eligible for treatment with obinutuzumab, we estimate based on Lythgoe et al. (54) that 80% of patients are class III, IV and V and that 79% of patients are adults (age≥18) based on Statistics Denmark (53). Based on statements from the Danish clinical expert consulted for this submission, we assume that 30% of new patients will receive treatment if a recommendation of usage is given by the Danish Medicines Council (DMC), i.e. app. 5 patients each year (26*0.8 *0.79*0.3=4.93). The clinical expert consulted also estimated that 3-5% of the prevalent patient population would receive treatment with obinutuzumab each year in connection with treatment of renal flares (5% assumed), i.e. app 18 patients each year (374*0.8*0.79*0.05=11.81). The estimated number of patients annually can be found in Table 2 below.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	17	17	17	17	17

3.3 Current treatment options

Current treatment in Danish clinical practice

In Danish clinical practice, the treatment of LN primarily follows guidelines aimed at preserving renal function, reducing disease activity, and preventing flares (55). The standard of care for Class III and IV LN (with or without Class V) typically involves initial induction therapy followed by long-term maintenance therapy.

Induction therapy

For newly diagnosed or relapsing LN patients, the initial induction therapy usually combines glucocorticoids with an immunosuppressive agent. The two main immunosuppressive regimens considered equivalent in terms of efficacy and safety are (55):

- **MMF-based regimen:** MMF is initiated at a dose of 2.0 g/day, with a gradual increase over 14 days to 3.0 g/day if tolerated. The prednisolone dosing begins with IV methylprednisolone 500 mg for 3 days, followed by oral prednisolone at 0.5 mg/kg/day. In cases of clinically severe disease, an initial intravenous (IV) dose of 0.7–1 mg/kg/day may be considered. The treatment goal is to taper the prednisolone dose to ≤ 10 mg/day by months 4–6.
- **CYC-based regimen:** The CYC-based induction regimen in Denmark follows the Euro-Lupus protocol, consisting of IV CYC administered at a dose of 500 mg every 14 days. This regimen is delivered in 6 doses over a period of 3 months, resulting in a total cumulative dose of 3 g. While oral CYC remains a therapeutic option, it is utilized less frequently in Danish clinical practice because clinical documentation for oral use is more limited compared to intravenous administration. The prednisolone dosing is identical to the MMF-based regimen.

Maintenance therapy

Following remission, maintenance therapy consists of MMF (e.g., 1–2 g/day) for at least 3 years or alternatively azathioprine (1–2 mg/kg/day). Immunosuppression is often required for longer periods, with doses adjusted based on clinical response. Prednisolone reduction typically begins at week 4; however, patients experiencing flares during tapering may require maintenance doses of 5–7.5 mg/day for 2–3 years. Monitoring is recommended every 2–4 weeks during the first 2–4 months, followed by lifelong follow-up at 3–6 month intervals (55).

Adjuvant therapy

Standard adjuvant therapy is provided to all patients to minimize disease activity and manage systemic risks (55).

Hydroxychloroquine (400 mg once daily) is the standard base therapy for all patients. For patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min, a 50% dose reduction is recommended.

Acetylsalicylic acid is indicated for all patients positive for anti-phospholipid antibodies. Patients who have experienced thromboembolic events should receive formal anticoagulation therapy.

Cholesterol-lowering treatment is recommended for patients with S-LDL cholesterol levels > 2.6 mmol/L. Given that the risk of cardiovascular events is 5–8 times higher in this population than in the general background population, this treatment may be considered even in the absence of dyslipidemia.

Management of refractory Disease
Treatment for refractory LN relies on clinical trials and expert recommendations due to a lack of systematic studies in refractory disease (55).

Belimumab is recommended by the national working group as an add-on to standard-of-care for refractory LN or frequent flares, supported by the BLISS-LN study.

Rituximab may be considered based on case series showing remission induction, though randomized trials as an add-on to MMF have not demonstrated increased efficacy. Tacrolimus can be considered if standard regimens fail, with the caveat that evidence is primarily from Asian populations and concerns exist regarding potential renal flares compared to MMF.

Expected prognosis with current treatments

As detailed in section 3.1, the prognosis for patients under the current Danish standard of care remains challenging. Despite the systematic use of induction and maintenance therapies, a significant proportion of patients continue to face high relapse rates and a 10–30% risk of progressing to ESKD within 15 years (55).

Furthermore, data from a Danish nationwide cohort study highlights the severity of the condition, observing a more than 10-fold increased risk of death in LN patients compared to the background population during the first five years post-diagnosis (19, 56). This is further supported by international evidence indicating that death directly attributable to kidney disease occurs in 5–25% of patients with proliferative LN within five years of onset (3).

In summary, these findings underscore a clear unmet need for therapies that can provide deeper and more sustained renal responses to alter the long-term disease trajectory and reduce both morbidity and mortality.

3.4 The intervention

Mechanism of action

Obinutuzumab is a humanized and glycoengineered, type II anti-CD20 IgG1 monoclonal antibody that binds to CD20 protein complexes on the B-cell surface. This binding results in potent B-cell depletion through antibody-dependent cellular cytotoxicity (ADCC),

antibody-dependent cellular phagocytosis (ADCP), direct cell death (DCD), and a low degree of complement-dependent cytotoxicity (CDC) (57-60).

The Fc region of obinutuzumab has been glycoengineered to enhance affinity for FcγRIII receptors on immune effector cells, such as macrophages, monocytes, and natural killer cells (59, 61-63). This modification results in significantly greater levels of cell death via ADCC and ADCP compared to non-glycoengineered antibodies (59, 61-63). Furthermore, obinutuzumab binds to CD20 in a type II conformation, which enables intra-tetramer binding and reduces CD20 internalization compared with type I antibodies. This specific binding prolongs engagement on the B-cell surface and induces higher levels of direct cell death while being less reliant on complement-dependent cytotoxicity than type I antibodies (59, 62-66).

Therapeutic rationale

The rationale for investigating obinutuzumab in LN is based on the hypothesis that the limited efficacy of type I anti-CD20 antibodies, such as rituximab, in previous trials was driven by incomplete B-cell depletion (67). In the Phase III LUNAR study, rituximab failed to demonstrate a statistically significant increase in overall renal response compared to placebo (67). However, post hoc analyses revealed that patients who achieved complete peripheral B-cell depletion were significantly more likely to achieve a CRR (unadjusted odds ratio 5.8; p=0.03) (68).

These findings suggest that the depth of depletion is a critical determinant of clinical response. Obinutuzumab was selected for investigation based on the premise that deeper and more sustained depletion of both peripheral and tissue-resident B cells would translate to improved renal outcomes (69, 70).

Clinical evidence of depletion

Preclinical data indicate that obinutuzumab depletes B cells in secondary lymphoid organs and tissues more effectively than type I antibodies. Data from the Phase II NOBILITY trial confirmed rapid depletion in humans, with 88% of patients in the obinutuzumab arm achieving complete depletion of total B-cells, memory B-cells, and plasmablasts from peripheral blood by Week 2 (71).

In the NOBILITY study, where no dosing occurred after Week 26, peripheral B-cell repletion was observed in the majority of patients by Week 104 (71). This finding informed the dosing regimen for the Phase III REGENCY trial, which includes maintenance infusions every 6 months for responders to maintain suppression and prevent the accrual of kidney damage (72).

The profound B-cell depletion observed in NOBILITY correlates with the improved clinical outcome demonstrated in the trial, contrasting with the results of previous trials using agents with less potent depletion profiles (e.g., the LUNAR study). Post hoc analyses of NOBILITY indicated that achieving sustained B-cell depletion through Week 52 was associated with higher renal response rates (73).

Regulatory status of short duration infusion (SDI)

On 29 January 2026, the Committee for Medicinal Products for Human Use (CHMP) issued a Positive Opinion for a Type II variation to include the administration of obinutuzumab as a short duration infusion (SDI) for patients with LN.

The clinical rationale for the SDI is based on a population pharmacokinetic model, safety data from clinical studies in patients with LN (Phase III study REGENCY, and Phase II study NOBILITY) and in patients with follicular lymphoma (Phase IV GAZELLE study and Phase III Study GALLIUM).

The implementation of SDI for obinutuzumab further reduces the treatment burden for patients and healthcare providers by shortening the time required for each maintenance session, while maintaining the proven efficacy and manageable safety profile demonstrated in the pivotal trials.

Overview of intervention (74)	
Indication relevant for the assessment	Gazyvaro in combination with MMF is indicated for the treatment of adult patients with active Class III or IV with or without Class V LN
ATMP	N/A
Method of administration	Intravenous (IV) infusion
Dosing	1000 mg per infusion Dose 1: Week 0 (initial infusion at day 1) Dose 2: Week 2 (2 weeks after dose 1) Dose 3: Week 24 Dose 4: Week 26 (2 weeks after dose 3) Dose 5 and thereafter: dose 5 should be administered 6 months after dose 4 and then every 6 months thereafter
Dosing in the health economic model (including relative dose intensity)	Obinutuzumab 1000 mg on weeks 1, 3, 25, 27 and 53. Subsequent infusions every 6 months starting at Week 80. Note that the model uses 1-based indexing where Day 1 is Week 1. This results in a 1-week offset compared to the clinical description (e.g., Week 2 becomes Week 3).
Should the medicine be administered with other medicines?	Obinutuzumab is intended as an add-on to standard-of-care treatment with MMF and glucocorticoids for adult patients with active Class III or IV lupus nephritis (with or without Class V).

Overview of intervention (74)	
Treatment duration / criteria for end of treatment	The patient's condition and response should be evaluated at Week 76 and beyond, and an appropriate risk benefit analysis should be made for continuation of therapy
Necessary monitoring, both during administration and during the treatment period	For patients receiving obinutuzumab, premedication with intravenous glucocorticoids, oral analgesic/anti-pyretics, and antihistamine medicine is recommended 30–60 minutes before infusion. Management of infusion-related reactions may require temporary interruption, reduction in the rate of infusion, or treatment discontinuation of obinutuzumab.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	One vial of 40 mL concentrate contains 1 000 mg obinutuzumab, corresponding to a concentration before dilution of 25 mg/mL.

IV, intraveneous; LN, Lupus nephritis; MMF, Mycophenolate mofetil; N/A, Not available.

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

Obinutuzumab is intended as an add-on to standard-of-care treatment with MMF and glucocorticoids for adult patients with active Class III or IV lupus nephritis (with or without Class V). It is given under specialist supervision with recommended premedication and administered on a twice-yearly maintenance schedule, which may reduce treatment burden and support adherence.

In Danish clinical practice, obinutuzumab will not replace existing therapies but complement MMF and glucocorticoids. Evidence from the REGENCY trial shows that its introduction enables a reduction in prednisone use, lowering glucocorticoid burden while maintaining disease control. No further changes to subsequent treatment lines are expected, and no additional diagnostic procedures beyond current practice are required.

3.5 Choice of comparator(s)

This application is based on the clinical evidence from the REGENCY trial, in which obinutuzumab was compared with placebo, both given in addition to standard-of-care therapy with MMF and glucocorticoids. This reflects current Danish clinical practice, where MMF in combination with glucocorticoids is the standard treatment in most

specialized treating facilities, and therefore represents the appropriate comparator for this assessment.

While overall treatment strategies are aligned, some differences exist in dosing regimens. In REGENCY, MMF was initiated at 1.5 g/day and increased to 2.0-2.5 g/day by Week 4, with this dose maintained throughout the trial. In Danish practice, MMF typically starts at 2.0 g/day, can be escalated to 3.0 g/day if tolerated, and is subsequently tapered to 1.0-2.0 g/day after remission, with maintenance therapy continued for at least 3 years. Glucocorticoid tapering in REGENCY was also more rapid (7.5 mg/day by Week 12) compared with Danish practice, where tapering is more gradual, aiming for a dose of ≤ 10 mg/day by months 4–6). From Week 12 onward, corticosteroid dosing becomes broadly comparable between the two settings.

These differences in MMF and glucocorticoid use may have some impact on transferability of the results. However, both regimens follow the same treatment principles, and placebo plus MMF and glucocorticoids remains representative of Danish standard of care.

Overview of comparator (75)	
Generic name	Mycophenolate mofetil (used off-label)
ATC code	Mycophenolate mofetil: L04AA06, Immunosuppressant
Mechanism of action	MMF is the 2-morpholinoethyl ester of mycophenolic acid, a selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase. By blocking the de novo synthesis of guanosine nucleotides, mycophenolic acid inhibits lymphocyte proliferation, as T- and B-cells rely on this pathway while other cells can use salvage routes. Beyond inosine monophosphate dehydrogenase inhibition, mycophenolic acid affects metabolic checkpoints in lymphocytes, shifting transcriptional activity from proliferation to catabolic and survival pathways, leading to anergy and antigen unresponsiveness in T-cells.
Method of administration	Oral
Dosing	MMF initiated at 1.5 g/day in Week 1, increased by 500 mg weekly to reach 2.0-2.5 g/day by Week 4, and maintained through Week 80
Dosing in the health economic model (including relative dose intensity)	2.5 mg per day
Should the medicine be administered with other medicines?	MMF is administered with steroids

Treatment duration/ criteria for end of treatment	Approximately 3 years
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	250 mg capsules: 1 carton of 100 capsules (in blister packs of 10); 1 carton of 300 capsules (in blister packs of 10); multipacks of 300 (3 packs of 100) capsules 500 mg film-coated tablets: 1 carton of 50 tablets (in blister packs of 10); multipacks of 150 (3 packs of 50) tablets

MMF, Mycophenolate mofetil.

Overview of comparator (76)	
Generic name	Prednisone
ATC code	H02AB07
Mechanism of action	Prednisone is a synthetic glucocorticoid prodrug metabolically activated in the liver to prednisolone. It functions as an immunomodulator by binding to cytoplasmic glucocorticoid receptors triggering a dual mechanism of the downregulation of pro-inflammatory transcription factors and the upregulation of anti-inflammatory mediators. This results in a systemic reduction in leukocyte infiltration, capillary permeability as well as a suppression of the immune system (77).
Method of administration	Oral
Dosing	Prednisone at 0.5 mg/kg/day in Week 1, tapered to 7.5 mg/day by Week 12 and 5 mg/day by Week 24
Dosing in the health economic model (including relative dose intensity)	Prednisone at 0.5 mg/kg/day in Week 1, tapered to 5 mg/day by Week 24
Should the medicine be administered with other medicines?	Prednisone should be given with MMF for LN
Treatment duration/ criteria for end of treatment	Approximately 3 years
Need for diagnostics or other tests (i.e. companion diagnostics)	No

Overview of comparator (76)	
Package size(s)	5 mg tablets: 1 glass containing 25 or 100 tablets 25 mg tablets: 1 glass containing 100 tablets

LN, Lupus nephritis; MMF, Mycophenolate mofetil

3.6 Cost-effectiveness of the comparator(s)

The comparator (MMF and prednisone) has not been evaluated by the Danish Medicines Council (DMC) in this setting. However, this combination represents the current standard of care in Denmark. Both MMF and prednisone are well-established, off-patent products with low acquisition costs. Consequently, it is a reasonable assumption that MMF and prednisone, as the Danish standard of care, can be considered cost-effective.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

All efficacy outcomes included in the application are defined in Table 3. Method of analysis, including dealing with missing values, is presented for each endpoint in section 6.1.4.

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Proportion of patients who achieved a CRR at Week 76 [REGENCY]	Week 76	CRR was defined as achievement of all the following: • Urinary protein-to-creatinine ratio (UPCR) < 0.5 g/g, based on a timed 24-hour urine collection • eGFR ≥ 85% of baseline • No occurrence of the following intercurrent events[a]: rescue therapy, treatment failure, death or early study withdrawal	Renal function (serum creatinine for eGFR) and proteinuria (24-hour UPCR) were assessed via blood and urine specimens analysed by a central laboratory to maintain blinding. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (78).

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Proportion of patients who achieved CRR with successful prednisone taper at Week 76 [REGENCY]	Week 76	Defined as achievement of CRR (as above) at Week 76 with the following: • No receipt of prednisone > 7.5 mg/day (or equivalent) from Week 64 through Week 76	Central laboratory results for renal parameters; medication records for corticosteroid use (78).
Proportion of patients who achieved a proteinuric response at Week 76 [REGENCY]	Week 76	Proteinuric response was defined as achievement of all of the following: • UPCR < 0.8 g/g • No occurrence of the following intercurrent events[a]: rescue therapy, treatment failure, death or early study withdrawal	Central laboratory analysis of urine samples (78).
Mean change in eGFR from baseline to Week 76 [REGENCY]	Week 76	N/A	Central laboratory analysis of serum creatinine (78) .
Proportion of patients who experienced death or renal related events through Week 76 [REGENCY]	Week 76	Defined as the proportion of patients with one or more of the following events: • Death • Treatment failure[b] • Worsening proteinuria, defined as a confirmed ≥ 50% increase in UPCR to a value ≥ 3 g/g • Worsening eGFR, defined as a confirmed ≥ 30% decrease in eGFR to a value < 60	Adverse event reporting (death/ESKD) and central laboratory monitoring (proteinuria/eGFR) (78).
Proportion of patients who achieved an ORR at Week 50 [REGENCY]	Week 50	ORR was defined as achievement of either CRR or PRR, with PRR defined as achievement of all the following: • ≥ 50% reduction in UPCR from baseline • UPCR < 1g/g (or < 3 g/g if the baseline UPCR was ≥ 3 g/g)	Central laboratory assessments at Week 50 (78)

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		• eGFR ≥ 85% of baseline, as calculated using the CKD-EPI equation • No occurrence of the following intercurrent events[a]: rescue therapy, treatment failure, death or early study withdrawal	
Change in FACIT-F scale from baseline to Week 76 [REGENCY]	Week 76	N/A	Collected on paper questionnaires and entered into the EDC system by site staff (78)
Total peripheral B-Cell (CD19) count [REGENCY]	Week 4, 12, 24, 50 and 76	Definition of depletion: Conventional flow cytometry assay (TBNK): CD19+ B cells < 10 cells/µL. High sensitivity flow cytometry assay (HSFC): CD19+ B cells < 0.441 cells/µL (Lower Limit of Quantification [LLOQ] of the assay	Blood samples were collected and analysed by a central laboratory using validated flow cytometry assays (TBNK and HSFC)
Time to LN flare from Week 24 through Week 76 [REGENCY]	Week 76	Defined as the time from Week 24 to the first occurrence of a diagnosed LN flare. A flare was diagnosed if one of the following conditions occurred: • eGFR decrease > 20% compared with Week 24 in patients with UPCR > 1 g/g and/or cellular casts. • UPCR increase (i) to > 1 g/g if Week 24 UPCR was < 0.2 g/g; (ii) to > 2.0 g/g if Week 24 UPCR was 0.2–1 g/g; or (iii) to doubling if Week 24 UPCR was > 1 g/g. • Receipt of rescue therapy, except for corticosteroid-only rescue.	Central laboratory assessments of serum creatinine (for eGFR) and UPCR. Investigator assessment of rescue therapy use and clinical judgment of flare.

* Time point for data collection used in analysis (follow up time for time-to-event measures).

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRR, complete renal response; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; LN, Lupus nephritis; LLOQ, Lower Limit of Quantification; ORR, overall renal response; PRR, Partial renal response; UPCR, urine protein-to-creatinine ratio.

[a]Intercurrent events for the study are the following: rescue therapy, treatment failure, study treatment discontinuation, death and early study withdrawal. [b]Treatment failure was present if any of the following criteria were met: (a) new ESKD or need for chronic dialysis or renal transplantation, (b) clinically significant, sustained worsening in UPCR and/or eGFR from Week 24 onward that led the investigator to conclude the patient had failed the randomized treatment regimen or (c) receipt of rescue therapy, except for glucocorticoid-only rescue.

Validity of outcomes

Primary endpoint

The composite endpoint of CRR is widely accepted by payers and key opinion leaders and is considered more stringent than the primary efficacy renal response (PERR) used in competitor trials (e.g., the BLISS-LN trial for belimumab (39)). In the REGENCY trial, CRR required a urine protein-to-creatinine ratio (UPCR) < 0.5 g/g, an eGFR ≥ 85% of baseline, and no intercurrent events (79).

This aligns with global guidelines (23, 28, 30) which identify achieving CRR as an important therapeutic goal associated with improved long-term kidney outcomes. In the DMC assessment of voclosporin (AURORA 1) (80), CRR served as the primary outcome; however, the REGENCY definition is more conservative regarding renal function preservation, requiring eGFR to remain ≥ 85% of baseline compared to the 20% confirmed decrease (effectively 80%) permitted in AURORA 1. Additionally, AURORA 1 integrated a mandatory low-dose steroid requirement directly into its primary endpoint, whereas in REGENCY, CRR with successful prednisone taper was evaluated as a key secondary efficacy endpoint (40, 79).

Secondary and supportive endpoints

The secondary and exploratory endpoints included in this application are established standards in LN clinical research. The majority of these endpoints were utilized by the DMC in the assessment of voclosporin (80).

- **Proteinuria thresholds:** UPCR thresholds of < 0.5 or < 0.8 g/g are validated surrogates for long-term renal outcomes and are increasingly recognized by payers as reliable indicators of durable benefit (81, 82).
- **Renal function (eGFR):** The CKD-EPI equation used in REGENCY is a standard, validated method for estimating renal function. Clinical data support eGFR preservation as a marker for long-term renal preservation (83).
- **Death or renal-related events:** This clinically meaningful secondary endpoint captures critical outcomes, providing a robust measure of disease progression.
- **Patient-reported outcomes (FACIT-F)**: The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Scale is a validated tool for assessing fatigue, which patients with LN identify as a severe and bothersome symptom (12, 84).
- **B-Cell depletion:** Peripheral B-cell depletion serves as a pharmacodynamic biomarker of the biological activity of obinutuzumab. In LN, deeper and more sustained depletion in both the blood and the tissues is associated with higher rates of renal response, as it effectively interrupts the autoimmune cycle driving glomerular inflammation (66).

- **Time to LN Flare (Week 24 through Week 76):** This endpoint is a critical measure of durable disease control, as renal flares are inherent to the natural history of LN and lead to irreversible nephron loss. Preventing these flares is essential because a single flare can reduce the glomerular filtration rate and significantly shorten kidney lifespan (1).

4. Health economic analysis

A cost utility analysis was developed from the perspective of the Danish health care sector to assess cost effectiveness of obinutuzumab for treatment of LN. Cost-effectiveness results are expressed as incremental costs per quality-adjusted life years (QALYs) and per life-years (LYs) gained. The model was created in Microsoft Office 365. The base-case and all scenario analyses weighed all outcomes equally for all patients regardless of the characteristics of those receiving or affected by the interventions (i.e., all QALYs are equal). The analysis utilized evidence primarily from the Phase III REGENCY study for estimating differences in treatment progression of obinutuzumab+MMF+ prednisone (PDS) versus placebo+MMF+PDS supplemented by other published literature to inform various model parameters.

4.1 Model structure

A de novo cohort multi-state Markov model was developed to synthesize all relevant clinical and economic evidence. This model structure is considered well-suited for chronic and progressive conditions like LN, as it effectively captures the dynamic progression of the disease considered over time. Due to LN impacting the function of the kidneys, the model is constructed around the different stages of chronic kidney disease (CKD), i.e. the following health states:

1. CKD1-3b: Active Disease (label: CKD_1_3b_AD)
2. CKD1-3b: Partial Response (label: CKD_1_3b_PR)
3. CKD1-3b: Complete Response (label: CKD_1_3b_CR)
4. CKD4: Active Disease (label: CKD_4_AD)
5. CKD4: Partial Response (label: CKD_4_PR)
6. CKD4: Complete Response (label: CKD_4_CR)
7. CKD5: Dialysis (label: CKD_5_D)
8. CKD5: Transplant (label: CKD_5_T)
9. Death (label: Death)

Where all patients remain in the *CKD_1_3b_AD* state at cycle 0, thus capturing the progression of disease from the early stages of the disease towards later states of kidney disease, where either dialysis or kidney transplantation are the only viable treatment options. KDIGO LN 24 guidelines (23) were used to inform criteria for inhabiting a given health state:

- CKD 1: eGFR >= 90 ml/min/1.73m2.
- CKD 2: eGFR 60 - 89 ml/min/1.73m2.
- CKD 3a: eGFR 45 - 59 ml/min/1.73m2.
- CKD 3b: eGFR 30 - 44 ml/min/1.73m2.
- CKD 4: eGFR 15 - 29 ml/min/1.73m2.
- CKD 5: eGFR < 15 ml/min/1.73m2

Mapping LN classes to CKD stages is not straightforward as the classification is based on the histological features seen in kidney biopsies. However, Class I and II LN often correspond to CKD Stage 1 or 2 where kidney function is typically well-preserved. Class III and IV LN indicate more significant inflammation and potential for substantial kidney damage meaning that patients can range from CKD stage 2-4. Membraneous lupus nephritis, i.e. Class V, can lead to nephrotic syndrome which can result in CKD stage 1-4. Progression in this state mainly depends on the response to treatment and control of symptoms. Class VI LN indicates advanced disease and sclerosis, often corresponding to CKD Stage 4 or 5 due to significant loss of kidney function.

A graphical illustration of the model can be found in Figure 1 below. Dotted lines refer to a functionality in the model which is not used in the base case).

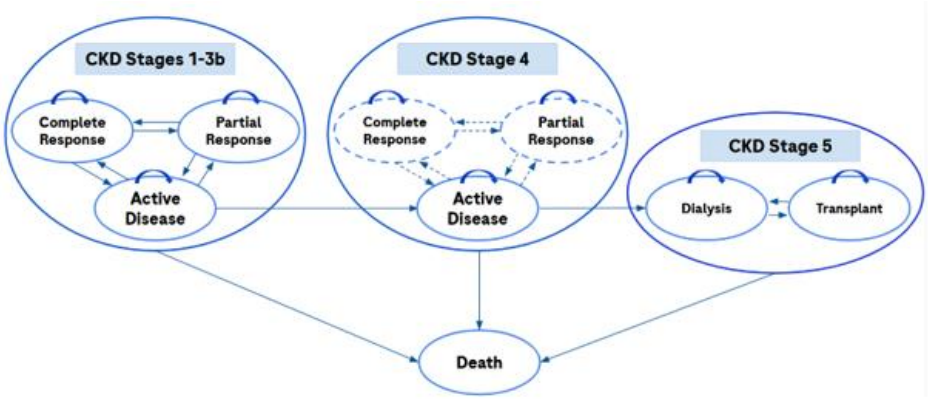

Figure 1. Graphical illustration of the model
CKD, Chronic kidney disease.

4.2 Model features

Table 4 provides an overview of the key features of the economic model.

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	Patients with International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 active Class III or IV with or without concomitant Class V LN	In accordance with trial population and EMA indication.

Model features	Description	Justification
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (99 years)	A life-time horizon was chosen in order to simulate long term outcomes, including the progression to end-stage renal disease (ESKD) and the impact of various treatment strategies over time. Most costs in LN are incurred in the late stages of kidney disease, where either dialysis or kidney transplantation are the only viable treatment options – these are considered key cost drivers for the model, hence a lifetime approach and the inclusion of these health states is important.
Cycle length	6 months	Cycle length is consistent with prior models for LN and capture the dynamic progression of lupus nephritis, including the transition between different stages of chronic kidney disease (CKD).
Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Obinutuzumab + MMF + PDS (Obi+MMF+PDS)	
Comparator(s)	MMF+PDS	Validated by Danish clinical expert (see section 14) and section 3.5
Outcomes	Complete renal response (CRR) and partial renal response (PRR, independent of CRR	Endpoint included in REGENCY and considered the best available endpoint for assessing the risk of disease progression

CKD, Chronic kidney disease; CRR, Complete renal response; DMC, Danish Medicines Council; ESKD, End-stage kidney disease; ISN/RPS , International Society of Nephrology/Renal Pathology Society; LN, Lupus nephritis; MMF, Mycophenolate mofetil; PDS, prednisone; PRR, Partial renal response.

5. Overview of literature

5.1 Literature used for the clinical assessment

This application is based on the head-to-head study, REGENCY (CA41705), which compares obinutuzumab with placebo for the treatment of patients with ISN/RPS 2003

Class III or IV with or without concomitant Class V LN treated with standard-of-care therapy consisting of MMF and glucocorticoids.

According to Danish treatment guidelines for LN, MMF plus prednisone is used as standard treatment for patients with LN. The treatment used in the REGENCY trial is very much in line with the current guidelines. MMF plus prednisone is considered a relevant comparator, and a literature review has therefore not been conducted.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Furie RA, Rovin BH, Garg JP, Santiago MB, Aroca-Martínez G, Zuta Santillán AE, Alvarez D, Navarro Sandoval C, Lila AM, Tumlin JA, Saxena A, Irazoque Palazuelos F, Raghu H, Yoo B, Hassan I, Martins E, Sehgal H, Kirchner P, Ross Terres J, Omachi TA, Schindler T, Pendergraft WF 3rd, Malvar A; REGENCY Trial Investigators. Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis. N Engl J Med. 2025 Apr 17;392(15):1471-1483. doi: 10.1056/NEJMoa2410965. Epub 2025 Feb 7. PMID: 39927615. (79)	REGENCY (CA41705)	NCT04221477	Start: 10/08/20 Completion: 02/28/31 Data cut-off 15/08/24 (Week 76) Future data cut-offs: Week 106, 132, 158, 184 and 210	Obinutuzumab compared with placebo in patients with International Society of Nephrology/Renal Pathology Society (ISN/RPS) Class III or IV with or without concomitant Class V LN when added on to standard-of-care therapy consisting of MMF and glucocorticoids.

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

N/A

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied

5.3 Literature used for inputs for the health economic model

A specific SLR was not conducted in connection with this submission to the DMC. While an SLR and targeted literature review for health economic input was conducted on behalf of Roche these were not particular to a Danish context and the SLR was scoped for several comparators not of relevance to Danish clinical practice. The health economic model associated with this submission use two of the sources also identified in the SLR and the targeted literature review. NICE's assessment of voclosporin for treatment of LN was identified in the SLR and Sugrue et al. was identified in the targeted literature review. These external references have been qualitatively assessed for relevance to a health economic model in a Danish context and used in this submission, since no other input sources of higher applicability/relevance has been identified.

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
NICE. Voclosporin with mycophenolate mofetil for treating lupus nephritis (TA882 (2023)) (85)	Transition probabilities and utilities not available from REGENCY	N/R (see above)	Section 8.2 and 10.3.4
Sugrue, D. M., Ward, T., Rai, S., McEwan, P. & Haalen, H. G. M. van. Economic Modelling of Sugrue DM, Ward T, Rai S, McEwan P, van Haalen HGM. Economic Modelling of Chronic Kidney Disease: A Systematic Literature Review to Inform Conceptual Model Design. Pharmacoeconomics. 2019 Dec;37(12):1451-1468. doi: 10.1007/s40273-019-00835-z. PMID: 31571136; PMCID: PMC6892339. (86)	Transition probabilities that are not available from REGENCY	N/R (see above)	Section 8.2
Eriksson D, Karlsson L, Eklund O, Dieperink H, Honkanen E, Melin J, et al. Health-related quality of life across all stages of autosomal dominant polycystic kidney disease. Nephrology Dialysis Transplantation. 2017;32(12):2106–11 (87)	HSUVs in dialysis and transplant state	Hand-searched (identified via DMCs assessment of imlifidase)	Section 10.3.4
Bilag til Medicinrådets anbefaling vedr. voclosporin som tillægsbehandling til lupus nefritis (80)	Disease management costs	Hand-searched	Section 11.4

6. Efficacy

6.1 Efficacy of obinutuzumab compared to placebo for patients with active Class III or IV (± V) lupus nephritis

6.1.1 Relevant studies

Study design

REGENCY (CA41705) is a phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of obinutuzumab in patients with International Society of Nephrology (ISN)/Renal Pathology Society (RPS) 2003 Class III or IV, with or without concomitant Class V, LN treated with standard-of-care therapy consisting of MMF and glucocorticoids (79). The study has completed enrolment, and the primary analysis has been completed (clinical cut-off date [CCOD]: 15 August 2024); the study is ongoing with an estimated completion date in 2031.

The REGENCY study consists of the following study periods: screening, blinded treatment, open-label treatment (OLT) and study follow-up. An overview of the study design for REGENCY is presented in Figure 2.

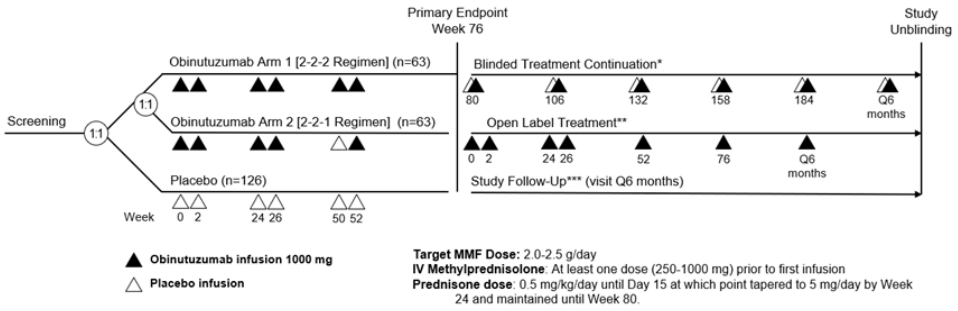

Figure 2 Study design of REGENCY.

IV, intravenous; MMF, mycophenolate mofetil. Patients with an adequate treatment response at Week 76 continue to receive blinded infusions every 6 months starting at Week 80, until study unblinding. Patients with inadequate treatment response at Week 76 or with loss of response during blinded treatment after Week 80 can enter open-label treatment. Patents are followed through Week 76 and for at least 12 months from the last dose of obinutuzumab or placebo.

Eligible patients were 18 to 75 years of age, met the American College of Rheumatology classification (ACR) criteria for systemic lupus erythematosus (SLE), and had active class III or IV LN, with or without concomitant class V disease (according to the classification of the International Society of Nephrology and the Renal Pathology Society), as confirmed on kidney biopsy performed either during or within 6 months before screening. Enrollment criteria included a UPCR of at least 1 (with protein and creatinine both measured in milligrams) based on 24-hour urine collection and antinuclear antibody

(ANA) positivity (i.e., an ANA titer of ≥1:80 on HEp-2 cells or ≥1 equivalent positive ANA test). Key exclusion criteria were an eGFR lower than 30 ml per minute per 1.73 m^2 of body surface area or end-stage kidney disease necessitating dialysis or transplantation, evidence of active infection, receipt of anti-CD20 therapy during or within 9 months before screening, and receipt of cyclophosphamide, tacrolimus, cyclosporine, or voclosporin therapy during or within 2 months before screening (79).

Blinded treatment up to Week 76

After screening, eligible patients were randomly assigned in a 1:1 ratio to receive intravenous infusions of obinutuzumab or matching placebo. Randomization was performed by means of a centralized interactive voice- and Web-based response system (IxRS) with the use of a permuted block design, with stratification according to geographic region (United States or Canada, Latin America or the Caribbean, or other) and race (Black or other).

Patients assigned to the obinutuzumab group were further randomized in a 1:1 ratio to receive obinutuzumab in one of two dose schedules (1000 mg on day 1 and at weeks 2, 24, 26, and 52, with or without an additional dose at week 50) (72). The rationale for including two dose schedules was exploratory and was aimed at gathering additional pharmacokinetic and pharmacodynamic data and exploring potential dose-related differences in efficacy to inform the selection of a dose regimen for long-term treatment (beyond week 76, which was used for the primary end point in this trial) (72).

Patients in both trial groups began receiving standard therapy with MMF and glucocorticoids at randomization (if not already receiving it) from the baseline visit (Day 1) onward (72). MMF was titrated by Week 4 to a target dose of 2.0-2.5 g/day in divided doses. For patients newly initiating MMF, the recommended initial dosage is 1.5 g/day given in divided doses with titration by 500 mg/week to 2.0-2.5 g/day by Week 4. MMF was maintained at the target dose through Week 80. Adjustments to MMF dosing were permitted in case of intolerance and adverse events. After Week 80, background immunosuppression could be adjusted at the discretion of the investigator. Investigators could continue MMF or switch to azathioprine (target dose: 2 mg/kg/day) as permitted by treatment guidelines (72). Oral glucocorticoids were initiated at a dose of 0.5 mg/kg (maximum 60 mg/day), tapered to a total daily oral maintenance dose of 5 mg at Week 24 and maintained at that dose through Week 80 (Figure 3) (72).

	Prednisone Dose (mg/day) [a]			
Days 2–14	30	40	50	60
Week 2	25	30	40	50
Week 4	25	25	30	40
Week 6	20	20	20	30
Week 8	15	15	15	20
Week 10	10	10	10	10
Week 12	7.5	7.5	7.5	7.5
Weeks 24–80	5	5	5	5

Figure 3 Prednisone tapering schedule through Week 80.

[a]Oral prednisone was started at 0.5 mg/kg/day (maximum 60 mg/day). Starting doses were rounded to the closest 10 mg increment or the nearest increment that is feasible based on the locally available oral prednisone dose strengths. An approximately equivalent dose of an oral corticosteroid with a similar duration of action may be substituted (72).

Treatment beyond Week 76

All patients were followed until Week 76 and for at least 12 months from the last dose of obinutuzumab or placebo (72). Patients who had an adequate response at Week 76 without a need for intensification of therapy or unmanageable treatment-emergent adverse events continued to receive a single blinded obinutuzumab 1000 mg or placebo infusion every 6 months, beginning at Week 80. The randomized treatment assignment was not revealed, and investigators and patients remained blinded during this period. Background immunosuppression, including doses of glucocorticoids and MMF, could be adjusted at the investigator's discretion beginning at Week 80. After Week 80, patients who, in the opinion of the investigator, experienced a loss of response and required intensification of therapy during continued blinded study treatment were eligible to receive OLT. Additionally, patients who, during continued blinded study treatment after Week 80, experience a loss of adequate response requiring intensification of therapy and without unmanageable treatment-emergent adverse events can initiate OLT once 60 days have elapsed from the most recent obinutuzumab or placebo infusion. Background immunosuppression, including doses of glucocorticoids and MMF, can be adjusted at the investigator's discretion beginning at OLT Day 1.

Patients who discontinued infusions prior to Week 76 still completed all visits through Week 76 according to the original schedule of activities before entering study follow-up. Patients who did not continue blinded infusions or enter open-label treatment based on the Week 76 assessment entered study follow-up. Patients who discontinued all infusions (blinded and open-label) beyond Week 76 also entered study follow-up. During study follow-up after Week 76, patients returned for regular assessments every 6 months (72).

Efficacy analysis

All efficacy analyses were carried out in the efficacy-evaluable population, including all randomized patients regardless of whether they received study drug. Patients were grouped according to randomized (assigned) treatment, rather than treatment received. Patients who received incorrect therapy are reported under the treatment arm to which they were randomized.

The primary efficacy endpoint was the proportion of patients who achieved CRR at Week 76, defined as achievement of all of the following (72, 79):

- A UPCR <0.5 based on a timed 24-hour urine collection
- An eGFR of ≥ 85% of the baseline value (calculated with the use of the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation)
- No occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal i.e., rescue therapy, treatment failure, death, or early trial withdrawal.

- Treatment failure was defined as end-stage kidney disease or the use of long-term dialysis or renal transplantation, receipt of rescue therapy (except for glucocorticoid-only rescue), or clinically significant and sustained worsening of the UPCR or eGFR beyond Week 24 that led the center investigator to conclude that the assigned regimen had failed.

The primary analysis was performed when all data was available for all patients who completed the Week 76 visit or discontinued the study prior to Week 76.

Key secondary endpoints include (72, 79):

- Proportion of patients who achieved CRR with successful prednisone taper at Week 76
- Proportion of patients who achieved a proteinuric response at Week 76
- Mean change in eGFR from baseline to Week 76
- Proportion of patients who experienced death or renal related events through Week 76
- Proportion of patients who achieved an ORR at Week 50
- Change in FACIT-F scale from baseline to Week 76
- Total peripheral B-Cell (CD19) count

Key exploratory endpoints include (72, 79):

- Time to LN flare from Week 24 through Week 76

Furthermore, patients were also offered an optional renal biopsy following the Week 76 assessment which could provide histologic evidence of disease activity or remission beyond the laboratory response measurements (72).

All secondary outcomes are listed in Table 8 and Appendix A. All definitions of outcome measures relevant for the application are listed in Table 3.

Safety analysis
Safety analyses up to Week 76 were performed using the safety-evaluable population, including patients who received any part of blinded infusion of obinutuzumab or placebo. Patients were grouped according to the treatment they actually received rather than the treatment assigned. Patients who received any part of an infusion of obinutuzumab as a study treatment (excluding obinutuzumab infusion received as a rescue therapy) even if not assigned to obinutuzumab treatment arm at randomization are reported under the obinutuzumab treatment arm.

The safety objective was to evaluate the safety of obinutuzumab (combined treatment groups) compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events (AEs), with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

- Characterization of adverse events of special interest (AESIs), including, among others, infusion-related reactions (IRRs), Grade 3–5 infections, drug related neutropenia and drug related thrombocytopenia.
- Change from baseline in targeted clinical laboratory test results.
- Change from baseline in targeted vital signs.

Table 8 Overview of study design for studies included in the comparison (72)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
REGENCY, NCT04221477 (79)	Phase III, randomized, double-blind, placebo-controlled study		Patients were in the age of 18 to 75 years, with the ACR criteria for SLE, and active class III or IV LN, with or without concomitant class V disease as confirmed on kidney biopsy performed either during or within 6 months before screening.	Patients in the obinutuzumab arm were randomly assigned in a 1:1 ratio to receive obinutuzumab in one of two dose schedules (1000 mg on day 1 and at weeks 2, 24, 26, and 52, with or without an additional dose at week 50). Patients in both trial groups began receiving standard therapy on Day 1 with MMF (titrated by Week 4 to a target dose of 2.0-2.5 g/day in divided doses. For patients newly initiating MMF, the recommended initial dosage was 1.5 g/day given in divided doses with titration by 500 mg/week to 2.0-2.5 g/day by Week 4) and prednisone (if not already receiving it). The target dose of prednisone was 7.5 mg/day by Week 12 and 5 mg/day by Week 24.	Patients in the placebo arm received placebo and similar standard therapy with MMF and prednisone as the dosing regimen described for the obinutuzumab arm.	Primary efficacy outcome • Proportion of patients who achieve a CRR at Week 76. Secondary efficacy outcomes • Proportion of patients who achieved CRR with successful prednisone taper at Week 76 • Proportion of patients who achieved a proteinuric response at Week 76 • Mean change in eGFR from baseline to Week 76 • Proportion of patients who experienced death or renal-related events through Week 76 • Proportion of patients who achieved an ORR at Week 50 • Change in FACIT-F scale from baseline to Week 76 • Change in log-transformed anti-double-stranded deoxyribonucleic acid (anti-dsDNA) titer at Week 50 • Change in complement C3 at Week 50 • Change in Systematic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) at Week 76

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						• Time to onset of CRR from baseline (Day 1) up to 80.3 weeks • Proportion of participants who achieve CRR with serum creatinine criteria at Week 76 • Number of participants with adverse events (AEs) up to Week 76 • Number of participants with adverse events of special interest (AESIs) up to Week 76 • Number of participants with anti-drug antibodies (ADAs) positive post-treatment up to approximately 11 years • Total peripheral B-Cell (CD19) count up to approximately 11 years • Concentration of obinutuzumab in serum up to approximately 11 years Follow-up period: All patients were followed until Week 76 and for at least 12 months from the last dose of obinutuzumab or placebo.

6.1.2 Comparability of studies

N/A. This section is not relevant as efficacy and safety are directly compared in the REGENCY study.

6.1.2.1 Comparability of patients across studies

Baseline characteristics of patients in the REGENCY study are listed in Table 9 (78, 79, 88). Baseline characteristics were generally balanced between the trial arms.

The median age of the patients was 30.0 years in the obinutuzumab arm and 31.0 years in placebo arm, and all patients were in the age group 18−65 years except for 1 patient in the placebo arm who was older than 65 years (78, 89). The proportion of females in the obinutuzumab arm and placebo arm was 84.4% and 84.6%, respectively. The median weight of patients in the obinutuzumab arm was 65.0 kg (36.7−106.3 kg) in the obinutuzumab arm and 65.5 kg (46.0−133.6 kg) in the placebo arm.

Some differences were observed for Ethnic group category where the majority of patients were Hispanic or Latino with 71 (52.6%) patients in the obinutuzumab arm and 85 (62.5%) patients in the placebo arm. Otherwise, 54 (40.0%) patients vs. 48 (35.3%) patients were Not Hispanic or Latino, 9 (6.7%) patients vs. 1 (0.7%) patients were Not Stated, and 1 (0.7%) patients vs. 2 (1.5%) patients were Unknown in the obinutuzumab arm and placebo arm, respectively. For Race or ethnic group, 65 (48.1%) patients in the obinutuzumab arm and 64 (47.1%) in the placebo arm were white. The proportions of other races were similar between the obinutuzumab arm and placebo arm with 25 (18.5%) vs. 26 (19.1%) American Indian/Alaska Native patients, 20 (14.8%) vs. 20 (14.7%) Black/African American patients, 9 (6.7%) vs. 7 (5.1%) Asian patients, 11 (8.1%) vs. 9 (6.6%) of Multiple Ethnicity, 4 (3.0%) vs. 6 (4.4%) unknown, and 1 (0.7%) vs. 4 (2.9%) Not Reported, respectively. Patients were initially stratified at randomization by region (United States and Canada vs. Latin America and the Caribbean vs. Other) and race (Black vs. Other), and the treatment arms were balanced with respect to these stratification factors. For race as stratification factor, 15 (11.1%) patients in the obinutuzumab arm and 17 (12.5%) patients in the placebo arm were black, and 120 (88.9%) patients in the obinutuzumab arm and 119 (87.5%) patients in the placebo arm were Other (79, 88). For Region as stratification factor, the majority of patients were from Latin America and the Caribbean with 77 (57.0%) patients in the obinutuzumab arm and 77 (56.6%) patients in the placebo arm. 20 (14.8%) patients vs. 20 (14.7%) patients were from United States and Canada, and 38 (28.1%) patients vs. 39 (28.7%) patients were Other in the obinutuzumab arm and placebo arm, respectively. 27 (20.0%) patients were from the European Union (EU) in the obinutuzumab arm and 26 (19.1%) patients in the placebo arm, and 108 (80.0%) patients in the obinutuzumab arm and 110 (80.9%) patients in the placebo arm were from non-EU countries (78, 89). The enrolled population was deemed to be sufficiently diverse, including populations with a high prevalence of LN and with a high risk of complications and death (79).

In the efficacy-evaluable population, treatment arms were generally well balanced with respect to baseline disease characteristics (eGFR, 24-hour UPCR, baseline LN class). Median serum creatinine level, eGFR and UPCR in the obinutuzumab arm were 0.79

mg/dL, 107 ml/min/1.73 m^2 and 2.13, respectively. Median serum creatinine level, eGFR and UPCR in the placebo arm were 0.74 mg/dL, 109 ml/min/1.73 m^2 and 2.76, respectively. In the obinutuzumab arm and placebo arm, 1 (0.7%) patient and 1 (0.7%) patient had an eGFR category <30 mL/min/1.73 m^2, 12 (8.9%) patients and 19 (14.0%) patients had an eGFR category of 30 to <60 mL/min/1.73 m^2, 26 (19.3%) patients and 20 (14.7%) patients had an eGFR category of 60 to <90 mL/min/1.73 m^2, and 96 (71.1%) patients and 96 (70.6%) patients had an eGFR category ≥90 mL/min/1.73 m^2, respectively. In the obinutuzumab arm 82 (61.2%) patients had a 24-hour UPCR <3 g/gram and 52 (38.8%) patients had a 24-hour UPCR ≥3 g/gram. In the placebo arm 74 (54.4%) patients had a 24-hour UPCR <3 g/gram and 62 (45.6%) patients had a 24-hour UPCR ≥3 g/gram. 57 (42.2%) patients in the obinutuzumab arm and 61 (44.9%) patients in the placebo arm had anti-dsDNA positive at >120 IU/mL. 77 (57.0%) patients in the obinutuzumab arm and 76 (55.9%) patients in the placebo arm had a C3 complement level <0.9 g/L. 32 (23.7%) patients in the obinutuzumab arm and 42 (31.1%) patients in the placebo arm had a C4 complement level <0.1 g/L. Median serum albumin were 35 g/L in both study arms. Median SLEDAI-2K score was 10 in the obinutuzumab arm and 12 in the placebo arm. Baseline classification of LN in the obinutuzumab arm and placebo were divided over Class III: 56 (41.5%) patients and 51 (37.5%) patients, Class IV: 79 (58.5%) patients and 85 (62.5%) patients, and concomitant Class V: 47 (34.8%) patients and 38 (27.9%) patients, respectively.

Of patients with previously diagnosed LN, there were 81 (60.0%) patients in the obinutuzumab group and 76 (55.9%) patients in the placebo group. As opposed to those with newly diagnosed LN, the median duration since the first LN diagnosis was 36.6 months (range, 0.4 to 330.4) in the obinutuzumab group and 34.3 months (range, 0.8 to 217.8) in the placebo group (79).

The majority of patients (157; 57.9%) had a prior history of LN (81 [60.0%] in the obinutuzumab arm and 76 [55.9%] in the placebo arm). Among these patients, the median duration of LN was 36.5 months (36.6 months in the obinutuzumab arm and 34.3 months in the placebo arm). Among patients who did not have a prior history of disease (114 patients [42.1%]), the median duration of LN calculated from the time of biopsy was 0.9 months in both arms. Other baseline characteristics, such as serum creatinine, serum albumin, serologic markers and SLEDAI-2K scores, were similar between treatment arms (see Table 9).

Table 9 Baseline characteristics of patients in the REGENCY study (78, 79, 88).

	REGENCY	
	Obinutuzumab (N=135)	**Placebo (N=136)**
Age, years		
Median (min-max)	30.0 (18-64)	31.0 (18-72)
Mean (SD)	33.0 (10.5)	32.7 (10.0)

REGENCY		
	Obinutuzumab (N=135)	**Placebo (N=136)**
Age group, years – n (%)		
<65	135 (100%)	135 (99.3%)
≥65	0	1 (0.7%)
Gender – n (%)		
Female	114 (84.4%)	115 (84.6%)
Male	21 (15.6%)	21 (15.4%)
Race or ethnic group – n (%)		
American Indian or Alaska Native	25 (18.5%)	26 (19.1%)
Asian	9 (6.7%)	7 (5.1%)
Black or African American	20 (14.8%)	20 (14.7%)
White	65 (48.1%)	64 (47.1%)
Multiple	11 (8.1%)	9 (6.6%)
Unknown	4 (3.0%)	6 (4.4%)
Not Reported	1 (0.7%)	4 (2.9%)
Race (stratification factor) – n (%) [a]		
Black	15 (11.1%)	17 (12.5%)
Other	120 (88.9%)	119 (87.5%)
Ethnic group – n (%)		
Hispanic or Latino	71 (52.6%)	85 (62.5%)
Not Hispanic or Latino	54 (40.0%)	48 (35.3%)
Not stated	9 (6.7%)	1 (0.7%)
Unknown	1 (0.7%)	2 (1.5%)
Region (stratification factor) – n (%)		

REGENCY		
	Obinutuzumab (N=135)	**Placebo (N=136)**
United States and Canada	20 (14.8%)	20 (14.7%)
Latin America and the Caribbean	77 (57.0%)	77 (56.6%)
Other	38 (28.1%)	39 (28.7%)
Region (EU/non-EU) – n (%)		
EU	27 (20.0%)	26 (19.1%)
Non-EU	108 (80.0%)	110 (80.9%)
Weight, kg		
Mean (SD)	66.3 (14.0)	68.3 (15.5)
Median (min-max)	65.0 (36.7 106.3)	65.5 (46.0 133.6)
Serum creatinine level – mg/dL [b]		
Median (min-max)	0.79 (0.34-3.75)	0.74 (0.27-4.39)
Mean (SD)	0.83 (0.39)	0.88 (0.48)
eGFR - mL/min/1.73 m²		
Median (min-max)	107 (15-164)	109 (13-166)
Mean (SD)	102.8 (29.3)	101.9 (32.2)
eGFR category – n (%)		
<30 mL/min/1.73 m²	1 (0.7%)	1 (0.7%)
30 to <60 mL/min/1.73 m²	12 (8.9%)	19 (14.0%)
60 to <90 mL/min/1.73 m²	26 (19.3%)	20 (14.7%)
≥90 mL/min/1.73 m²	96 (71.1%)	96 (70.6%)
24-hour UPCR – g/gram [c]		
Median (min-max)	2.13 (0.2-21.6)	2.76 (0.1-13.3)
Mean (SD)	3.14 (2.99)	3.53 (2.76)

REGENCY		
	Obinutuzumab (N=135)	**Placebo (N=136)**
24-hour UPCR – n (%)		
<3 g/gram	82 (61.2%)	74 (54.4%)
≥3 g/gram	52 (38.8%)	62 (45.6%)
Anti-dsDNA positive at >120 IU/mL – n (%)	57 (42.2%)	61 (44.9%)
C3 complement level <0.9 g/L – n (%)	77 (57.0%)	76 (55.9%)
C4 complement level <0.1 g/L – n (%) [d]	32 (23.7%)	42 (31.1%)
Serum albumin – g/L		
Median (min-max)	35 (16-46)	35 (15-46)
Mean (SD)	34.7 (6.2)	34.0 (6.3)
Baseline lupus nephritis class – n (%)		
Class III	56 (41.5%)	51 (37.5%)
Class IV	79 (58.5%)	85 (62.5%)
Concomitant class V	47 (34.8%)	38 (27.9%)
Previously diagnosed lupus nephritis – n (%) [e]	81 (60.0%)	76 (55.9%)
Median duration of LN for patients who had prior history of LN — months (min-max)	36.6 (0.4-330.4)	34.3 (0.8-217.8)
Median duration of LN calculated from time to biopsy for patients who did not have prior history of LN — months (min-max)	0.9 (0.2-6.8)	0.9 (0.2-5.0)
SLEDAI-2K score [f]		
Median (min-max)	10 (4-83)	12 (2-35)
Mean (SD)	12.1 (8.1)	12.4 (6.7)

Abbreviations: eGFR, estimated glomerular filtration rate; LN, Lupus nephritis; UPCR, 24-hour Urine Protein/Creatinine Ratio; dsDNA, double stranded DNA; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000

[a] Race and ethnic group were determined on the basis of patient-reported data in the electronic case-report forms. At the time of enrollment, Black or other (a randomization stratification factor) were the only two randomization options for race in the IxRS system. After enrollment, additional information on race and ethnicity was collected via electronic case report forms with further options. One patient who was registered

as Black in the IxRS system reported being multiracial in the case-report form, and nine patients who were registered as other in the IxRS system reported being Black or African American in the case-report form.
[b] To convert serum creatinine to micromoles per liter, multiply by 88.4.
[c] The urinary protein-to-creatinine ratio (UPCR) was based on 24-hour urine collection, with protein and creatinine both measured in milligrams. Data were missing for one patient in the obinutuzumab group.
[d] Data on C4 complement level were missing for one patient in the placebo group.
[e] With respect to the patients enrolled and their lupus nephritis disease states in the obinutuzumab and placebo groups, 60.0% (n = 81) and 55.9% (n = 76) of patients had prior histories of lupus nephritis with median (range) durations of lupus nephritis of 36.6 (0.4 to 330.4) and 34.3 (0.8 to 217.8) months in the obinutuzumab and placebo groups, respectively. The remaining patients (40.0% [n = 54] and 44.1% [n = 60] in the obinutuzumab and placebo groups, respectively) did not have prior histories of lupus nephritis but were newly diagnosed based on native kidney biopsies. For these patients, durations of lupus nephritis from the time of native kidney biopsy to randomization were medians (range) of 0.9 (0.2 to 6.8) and 0.9 (0.2 to 5.0) months in the obinutuzumab and placebo groups, respectively.
[f] SLEDAI-2K range from 0 to 105, with higher scores indicating greater disease activity. Data were missing for three patients in the placebo group.

6.1.3 Comparability of the study population with Danish patients eligible for treatment

The demographic characteristics of the Danish LN population are derived from the nationwide cohort study by Hermansen et al (2016) (52). LN is primarily a condition of premenopausal women, with incidence peaking before age 50. After age 60, the incidence rates between men and women converge and show no significant difference.

The population is characterized by a strong female predominance; in the identified cohort, 76% of patients were female and 24% were male. The median age for the total LN population is 42 years (interquartile range [IQR]: 31–56). Females typically present earlier, with a median age of 41 years (IQR: 30–51), whereas males present later with a median age of 51 years (IQR: 35–67) (52).

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (52)	Value used in health economic model (79)
Female	76%	85%
Age, all, yrs	42 (IQR 31-56)	42
Age, female, yrs	41 (IQR 30-51)	N/A
Age, males, yrs	51 (IQR 35-67)	N/A

6.1.4 Efficacy – results per REGENCY (CA41705)

This section presents results on the following outcomes from REGENCY (CA41705):

- Primary efficacy endpoint
  - CRR at Week 76
- Secondary efficacy endpoints
  - CRR with successful prednisone taper at Week 76
  - Proteinuric Response at Week 76

    - Mean change in eGFR from baseline to Week 76
    - Death or renal-related events through Week 76
    - ORR at Week 50
    - Mean change in FACIT-F Scale from baseline to Week 76
    - Total peripheral B-Cell (CD19) count
- Exploratory efficacy endpoints
    - Time to LN flare from Week 24 through Week 76
    - PRR at Week 76 (evaluated post hoc)

Multiplicity adjustment (hierarchical testing)

To control the overall family-wise Type I error rate at a two-sided α=0.05 across the primary and key secondary endpoints, a fixed sequence testing procedure combined with a fallback method was utilized.

- Testing began with the primary endpoint (CRR).
- If successful, testing proceeded to the first key secondary endpoint (CRR with successful prednisone taper).
- If the first key secondary endpoint was significant, the alpha (α=0.05) was split between the subsequent endpoints: Proteinuric Response (α=0.04) and Change in eGFR (α=0.01). This allowed for "recycling" of alpha if specific endpoints met statistical significance, maximizing the power to detect effects in lower-tier endpoints like Death or renal-related events.

For full details regarding the statistical hypothesis testing, power calculations, censoring rules, and sensitivity analyses (including tipping point analyses), please refer to the Statistical Analysis Plan (SAP) (90).

Complete renal response (CRR) at Week 76
The primary endpoint was the proportion of patients achieving a CRR at Week 76. CRR was defined as a UPCR < 0.5 g/g based on a timed 24-hour urine collection, an eGFR ≥ 85 % of baseline (calculated by the CKD-EPI equation), and no intercurrent events (rescue therapy, treatment failure, study treatment discontinuation, death or early study withdrawal).

The analysis was performed in the efficacy-evaluable population, defined as all randomized patients, regardless of treatment received, grouped by assigned treatment arm. The primary comparison between obinutuzumab and placebo was based on a Cochran–Mantel–Haenszel test stratified by race (Black vs other) and region (United States and Canada vs Latin America and Caribbean vs Other). Missing data were handled by multiple imputation.

Obinutuzumab plus standard-of-care demonstrated a statistically significant and clinically meaningful improvement in the rate of CRR versus placebo plus standard-of-care at Week 76.

CRR was achieved by 46.4% of patients treated with obinutuzumab compared with 33.1% in the placebo arm (adjusted difference 13.4%, 95% confidence interval [CI] 1.95 to 24.84; p = 0.0232) (78, 79). This confirms a clinically relevant absolute increase of around one in eight patients achieving CRR when obinutuzumab is added to MMF and glucocorticoids. The treatment effect was consistent across key subgroups including high baseline disease activity (UPCR ≥ 3 g/g, low complement, positive anti-dsDNA) and ethnic groups.

CRR with successful prednisone taper at Week 76
This endpoint assessed the proportion of patients achieving CRR (as defined above) while maintaining a prednisone dose ≤ 7.5 mg/day (or equivalent) between Weeks 64 and 76. The same statistical approach and imputation strategy were used as for the primary analysis.

A significantly higher proportion of patients achieved CRR with successful prednisone taper in the obinutuzumab arm than in the placebo arm (42.7% versus 30.9%, adjusted difference 11.9%, 95% CI 0.57 to 23.18; p = 0.0421) (78, 79). This demonstrates that obinutuzumab not only increases renal response rates but also enables clinically relevant glucocorticoid sparing, supporting guideline recommendations for minimising steroid exposure.

Proteinuric response at Week 76
Proteinuric response was defined as achievement of UPCR < 0.8 g/g without intercurrent events. The endpoint was analysed in the efficacy-evaluable population using the Cochran–Mantel–Haenszel test stratified by race and region, with multiple imputation for missing data.

Obinutuzumab was superior to placebo for achieving proteinuric response at Week 76 (55.5% vs 41.9%; adjusted difference 13.7%, 95% CI 2.01 to 25.36; p = 0.0227) (78, 79). These data indicate that obinutuzumab produces a faster and more complete reduction in proteinuria, a validated surrogate for long-term renal survival.

Mean change in eGFR from baseline to Week 76
Change in eGFR from baseline was analysed using an analysis of covariance model adjusted for baseline eGFR, treatment group, race and region. Missing values were handled using multiple imputation.

The mean change in eGFR favoured obinutuzumab (+ 2.3 mL/min/1.73 m²) compared with a decline in the placebo arm (– 1.5 mL/min/1.73 m²), yielding an adjusted between-group difference of 3.8 mL/min/1.73 m² (95 % CI – 1.84 to 9.51; p = 0.1842) (78, 79). Although not statistically significant within the hierarchical testing sequence, the numerical difference supports preservation of kidney function with obinutuzumab over 76 weeks.

Death or renal-related events through Week 76
This composite endpoint included death, treatment failure, sustained proteinuria worsening (≥ 50 % increase to ≥ 3 g/g), or confirmed eGFR decline (≥ 30 % to < 60 mL/min/1.73 m²). Proportions were compared between treatment arms using the

Cochran–Mantel–Haenszel test stratified by race and region, with multiple imputation for missing data.

Fewer patients experienced death or renal-related events in the obinutuzumab arm than in the placebo arm (18.9% vs 35.6%; adjusted difference –16.8%, 95% CI –27.50 to –6.23; p = 0.0026). This represents a clinically meaningful reduction in the risk of unfavourable kidney outcomes over 18 months of therapy (78, 79).

Overall renal response (ORR) at Week 50
Overall renal response was defined as achievement of either CRR or partial renal response (PRR). PRR required a ≥ 50 % reduction in UPCR from baseline to < 1 g/g (or < 3 g/g if baseline ≥ 3 g/g), eGFR ≥ 85 % of baseline, and no intercurrent events. Comparison between treatment arms used the same statistical approach as other binary endpoints.

At Week 50, obinutuzumab produced numerically higher overall renal response rates (59.1% vs 50.7%; adjusted difference 8.4%, 95% CI –3.41 to 20.12; p = 0.1670). While not statistically significant in the hierarchical testing sequence, this trend supports the consistent treatment effect across composite renal outcomes (78, 79).

Change in FACIT-F (Fatigue) from baseline to Week 76
Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale. Changes from baseline were analysed using ANCOVA adjusted for baseline score, race and region.

Mean improvement in fatigue was slightly greater with obinutuzumab (+ 1.8 points) compared with placebo (+ 3.1 points); the between-group difference (– 1.4 points; 95% CI –3.41 to 1.20; p = 0.2991) was not statistically significant. Overall, fatigue improved modestly in both arms during disease control, with no evidence of treatment-related detriment to patient-reported fatigue (78, 79).

Total peripheral B-cell (CD19) Count
The effect of obinutuzumab on levels of CD19-positive B cells in blood was assessed through Week 76 using two complementary methods to characterize the depth and duration of suppression. The analysis was conducted in the safety-evaluable population. B-cell depletion was defined according to the following thresholds:

- Conventional Flow Cytometry (TBNK assay): CD19-positive B cells < 10 cells/µL, used to define the standard clinical "B-cell depletion" threshold.
- High-Sensitivity Flow Cytometry (HSFC): CD19-positive B cells below the limit of quantitation (BLQ) of CD19-positive B cells < 0.441 cells/µL, utilized to quantify minimal residual B cells and characterize the specific depth of depletion.

Results are summarized descriptively (mean and median) over time by treatment arm

The TBNK assay demonstrated that obinutuzumab treatment resulted in rapid and sustained peripheral B-cell depletion in most patients, with average levels remaining at

or below the clinical threshold of 10 cells/µL threshold throughout the 76-week treatment period. By Week 4, [redacted] of patients treated with obinutuzumab achieved B-cell depletion compared with [redacted] in the placebo arm. This high rate of depletion was maintained at every subsequent assessment timepoint through Week 76 ([redacted]) (78).

The HSFC assay demonstrated that obinutuzumab induced "deep" depletion, where B-cell levels fell BLQ of < 0.441 cells/µL. This significantly distinguished the depth of response compared with placebo. By Week 4, 78.0% of obinutuzumab-treated patients reached undetectable B-cell levels compared with 1.7% in the placebo arm. The proportion of patients in the obinutuzumab arm achieving deep depletion remained consistently high across the remaining primary study visits (Week 24: 60.2% vs. 0.8% by Week 24; 66.9% vs. 1.7% by Week 50; 70.4% vs. 1.7% by Week 76) (78).

Time to LN flare from Week 24 through Week 76

Time to first LN flare was evaluated as a pre-specified exploratory endpoint starting from Week 24. A flare was diagnosed if any of the following criteria were met:

- eGFR decrease > 20% compared with Week 24 in patients with UPCR > 1 g/g and/or cellular casts
- UPCR increase
    - to > 1 g/g if Week 24 UPCR was < 0.2 g/g, or
    - to > 2.0 g/g if Week 24 UPCR was 0.2−1 g/g, or
    - to doubling if Week 24 UPCR was > 1 g/g
- Receipt of rescue therapy, except for glucocorticoid-only rescue

Efficacy comparisons were performed using a Cox proportional-hazards model stratified by race and region. Summary statistics, including the median time to flare and percentiles, were derived from Kaplan-Meier (KM) estimates. Confidence intervals (95% CI) for the median were computed using the Brookmeyer and Crowley method.

Patients who withdrew from the study prior to experiencing an event were censored at the time of withdrawal. Patients who completed the 76-week blinded treatment period without a flare were censored at the upper limit of the Week 76 visit window.

The incidence of renal flares was numerically lower with obinutuzumab compared to placebo ([redacted] The hazard ratio (HR) for flare was [redacted], supporting a reduced risk of renal flares in favour of obinutuzumab. These results suggest that obinutuzumab provides a more durable renal response and reduces the likelihood of disease reactivation following initial control (78).

Additionally, the KM plot for time to flare demonstrated a clear separation in favour of the obinutuzumab arm starting at Week 24 and continuing through Week 76 (Figure 4) (78).

[redacted]

Figure 4 Kaplan–Meier plot of time to lupus nephritis flare from Week 24 through Week 76. Efficacy-Evaluable Population

Partial renal response (PRR) at Week 76

Partial Renal Response (PRR) independent of CRR was an exploratory endpoint evaluated post hoc to establish transition probabilities for the economic Markov model. This analysis was conducted using the efficacy-evaluable population (91).

PRR is defined as the achievement of all of the following criteria:

- ≥ 50% reduction in UPCR from baseline
- UPCR <1 g/g (or <3 if the baseline UPCR was ≥ 3)
- eGFR ≥ 85% of baseline, as calculated using the CKD-EPI equation
- No occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal.

Patients who experienced the intercurrent event of study treatment discontinuation were evaluated using their observed data under a treatment policy strategy. Missing data were addressed via multiple imputations using the fully conditional specification (FCS) predicted mean matching method. A Cochran-Mantel-Haenszel test was performed, stratified by race and region. The adjusted difference (common risk difference) and its 95% CI based on stratified Newcombe CI were calculated using Mantel-Haenszel weights.

At Week 76, PRR independent of CRR was achieved by [redacted] of patients in the obinutuzumab arm compared with [redacted] in the placebo arm. The adjusted difference was [redacted]) (91).

Summary

Across the primary and key secondary endpoints, obinutuzumab in combination with standard immunosuppression significantly improved rates of CRR and proteinuria reduction and enabled clinically meaningful steroid tapering. Trends towards preserved eGFR and fewer renal events support the long-term renal protective effect of deep B-cell depletion. The reduction in LN flares further indicates enhanced disease control and durability of response through 76 weeks. These outcomes are consistent with DMC criteria for clinically meaningful benefit in chronic progressive renal disease.

7. Comparative analyses of efficacy

N/A. Table 11 is completed according to DMC guidelines.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

Table 11 Results from the comparative analysis of obinutuzumab vs. placebo for LN patients

Outcome measure	Obinutuzumab (N=135)	Placebo (N=136)	Result
CRR at Week 76	46.4% (95 % CI: 37.95, 54.86)	33.1% (95 % CI: 25.18, 41.00)	13.4% (95 % CI: 1.95, 24.84; p = 0.0232)
CRR with Successful Prednisone Taper at Week 76	42.7% (95 % CI: 34.32, 51.09)	30.9% (95 % CI: 23.12, 38.65)	11.9% (95 % CI: 0.57, 23.18; p = 0.0421)
Proteinuric Response at Week 76	55.5% (95 % CI: 47.09, 63.95)	41.9% (95 % CI: 33.62, 50.20)	13.7% (95 % CI: 2.01, 25.36; p = 0.0227)
Mean Change in eGFR from Baseline to Week 76	2.3 mL/min/1.73 m^2 (SE: 2.713)	– 1.5 mL/min/1.73 m^2 (SE: 2.706)	3.8 mL/min/1.73 m^2 (95 % CI: – 1.84; 9.51; p = 0.1842)
Death or Renal-Related Events through Week 76	18.9% (95 % CI: 12.11, 25.61)	35.6% (95 % CI: 27.50, 43.78)	– 16.8% (95 % CI: – 27.50, –6.23; p = 0.0026)
ORR at Week 50	59.1% (95 % CI: 50.80, 67.43)	50.7% (95 % CI: 42.16, 59.22)	8.4% (95 % CI: −3.41, 20.12; p = 0.1670)
Change in FACIT-F from Baseline to Week 76	1.8 points (SE: 1.22)	3.1 points (SE: 1.21)	– 1.4 points (95 % CI: −3.89, 1.20; p = 0.2991)
Total peripheral B-Cell (CD19) count at Week 76 (TBNK assay)	[redacted]	[redacted]	[redacted]
Total peripheral B-Cell (CD19) count at Week 76 (HSFC assay)	[redacted]	[redacted]	[redacted]
Time to Lupus Nephritis Flare from Week 24 through Week 76	[redacted]	[redacted]	[redacted]

CI, Confidence interval; CRR, Complete renal response; eGFR, Estimated glomerular filtration rate; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HR, Hazard ratio, NE, not estimable; ORR, overall renal response; SE, standard error.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

As the health economic analysis is a Markov model presentation of efficacy data is provided in section 8.1.3 describing transition probabilities (TPs).

8.1.1 Extrapolation of efficacy data

N/R

8.1.1.1 Extrapolation of [effect measure 1]

N/R

Table 12 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	

8.1.2 Extrapolation of [effect measure 2]

N/R

8.1.3 Calculation of transition probabilities

The below table provides an overview of the transition probabilities in the model where probabilities differ between the invention and the comparator arm namely the transitions from the initial state *CKD_1_3b_AD* towards the health states *CKD_1_3B_PR* and *CKD_1_3B_CR*. These transitions were informed by utilizing CRR and PRR rates from the REGENCY trial evaluated at week 76. To convert these into the cycle length of the model, an exponential distribution for extrapolation as per Briggs, Claxton , & Sculpher, 2006 (92) was used thus assuming the hazard rate to be constant:

$$Transition\ probability = 1 \quad \exp\left(\quad \left(\frac{-\ln(1-X)}{Y}\right) * Z\right)$$

Where X represents either CRR or PRR from REGENCY and Y is the timepoint of evaluating efficacy (1.5 years). Z represents the model cycle length in years (0.5). The PRR and CRR rates from REGENCY are presented in section 6.1.4.

Further transition probabilities, that are estimated in the model, but are similar between the intervention and the comparator, are provided in section 8.2. The transition matrices providing all the transition probabilities of the model can also be found in Table 14 below. A Markov trace for the intervention and comparator can be found in the cost effectiveness model (CEM) (see sheet named "Markov Model").

Table 13 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
CKD_1_3b_AD	CKD_1_3b_PR	PRR response rate obtained in REGENCY for intervention arm and comparator arm respectively at week 76 converted into 6 month probability	REGENCY
	CKD_1_3b_CR	CRR response rate obtained in REGENCY for intervention arm and comparator arm respectively at week 76 converted into 6 month probability	REGENCY
	CKD_1-3b (AD)	Residual (1 minus other probabilities)	REGENCY

CRR, Complete renal response; PRR, Partial renal response

8.2 Presentation of additional efficacy data from REGENCY, TA882 and Sugrue et al.

Table 14 provides the transition probability matrix for the intervention and comparator. Transition probabilities that are listed as a number are similar between the two treatment arms, and otherwise differ. References for each TP can also be found in this section along with further description of external literature used. Below the table, a list is provided with explanation of each TP.

Table 14. Overview of all transition probabilities in the health economic model.

	CKD st. 1-3b (AD)	CKD st. 1-3b (PR)	CKD st. 1-3b (CR)	CKD st. 4 (AD)	CKD st. 4 (PR)	CKD st. 4 (CR)	CKD st. 5 Dialysis	CKD st. 5 Transplant	Death
CKD st. 1-3b (AD)	Residual (f)	per REGENCY (a)	per REGENCY (a)	0.031 (b)	0	0	0	0	[redacted]

CKD st. 1-3b (PR)	[redacted]	[redacted]	[redacted]	0	0	0	0	0	[redacted]
CKD st. 1 3b (CR)	[redacted]	[redacted]	[redacted]	0	0	0	0	0	[redacted]
CKD st. 4 (AD)	0	0	0	0.97 (f)	0	0	0.033 (e)	0	0.0392 (j)
CKD st. 4 (PR)	0	0	0	0 (g)	0 (g)	0 (g)	0	0	0.0392 (j)
CKD st. 4 (CR)	0	0	0	0 (g)	0 (g)	0 (g)	0	0	0.0392 (j)
CKD st. 5 (Dialysis)	0	0	0	0	0	0	0.77 (f)	0.23 (h)	0.0847 (j)
CKD st. 5 Transplant	0	0	0	0	0	0	0.04 (i)	0.96 (f)	0.0262 (j)

CKD, Chronic kidney disease.

(a) Calculated on the basis of PRR and CRR rates from REGENCY for each treatment arm (see 6.1.4 and Table 13)
(b) Per TA882 (85) where it was estimated, based on KOL feedback, that patients have a 6% probability of transitioning to CKD 3b-4 per year.
(c) Pooled analysis of REGENCY using R msm package to estimate TP based on transition counts
(d) Pooled analysis of REGENCY using R msm package to estimate TP based on transition counts
(e) Sugrue et al. 2019 (86)
(f) Remaining probability to stay in current state
(g) Set to 0, i.e. assume that response does not occur when having reached CKD stage 4
(h) Per TA882 (85) – where EAG estimated a 65% transplantation rate every two years (23.08% every 6 months).
(i) Sugrue et al. 2019 (86)
(j) Sugrue et al. 2019 (86)

8.2.1 Transitions from CKD 1-3b

CR, PR and AD within the CKD 1-3b health states are explicitly response-based structures for modelling LN. They are not simply a categorization of CKD severity, but rather reflect a patient's kidney health status in response to LN and its treatment.

Transitions from *CKD 1-3b_PR* and *CKD 1-3b_CR* to other health states were based on a pooled analysis of REGENCY, where count data was used to estimate separate multi state

Markov model (transitions (c) and (d) mentioned above). Individual patient movements throughout defined health states were counted at three defined post baseline timepoints: 24 weeks, 52 weeks and 76 weeks. The data was also used to estimate transitions to death.

Patients within *CKD 1-3 b_PR* and *CKD 1-3 b_CR* cannot transition to the CKD-4 health states. According to Roche clinical expert view (93), if the patient is responding to the treatment (that is, they are in PRR or CRR) we can assume that their disease is not active. The correlation between these is strong, but not perfect. This means that there are some patients who will progress to CKD Stage 4 from CRR or PRR, but these will not be the majority, rather only a few. There are no observable cases of this in REGENCY and also none was cited in the Voclosporin NICE submission (85), so the simplification assumption that transitions from CRR or PRR to CKD Stage 4 are not possible in the model, does not seem to be too limiting. In LN, AD can only be confirmed via kidney biopsy. As this is a risky procedure, it is not considered reasonable to request a kidney biopsy if the patient is doing well, i.e. kidney disease is under control.

It is assumed that treatment effect is maintained over time. The model does however incorporate a function where treatment waning can be applied for sensitivity analysis purposes. If this is selected, the user needs to provide further input to define what the waning period is. It is defaulted that the treatment waning will start on the next cycle after the treatment duration finishes.

Table 15. Transitions from CKD stages 1-3b

Transition	Transition Probability	References
CKD st. 1-3b (AD) → CKD st. 1-3b (PR)	Obi+mmf+pds [redacted] Mmf+pds: [redacted]	From REGENCY PRR and CRR response rates (see Table 13)
CKD st. 1-3b (AD) → CKD st. 1-3b (CR)	Obi+mmf+pds [redacted] Mmf+pds: [redacted]	From REGENCY PRR and CRR response rates (see Table 13)
CKD 1-3b (PR) → CKD 1-3b (CR)	[redacted]	Msm model using REGENCY IPD (see Appendix K)
CKD 1-3b (PR) → CKD 1-3b (AD)	[redacted]	Msm model using REGENCY IPD
CKD 1-3b (PR) → CKD 1-3b (PR)	[redacted]	Calculated (1 – other probs)
CKD 1-3b (CR) → CKD 1-3b (AD)	[redacted]	Msm model using REGENCY IPD (see Appendix K)
CKD 1-3b (CR) → CKD 1-3b (PR)	[redacted]	Msm model using REGENCY IPD (see Appendix K)
CKD 1-3b (CR) → CKD 1-3b (CR)	[redacted]	Calculated (1 – other probs)

CKD 1-3b (AD) → CKD 4 (AD)	3.05%	Per TA882 (85): KOL expert feedback. Probability of 6% transitioning to CKD 3b-4 per year (3.05% per cycle).
CKD 1-3b (CR) → Death	[redacted]	Msm model using REGENCY IPD (see Appendix K)
CKD 1-3b (PR) → Death	[redacted]	Msm model using REGENCY IPD (see Appendix K)
CKD 1-3b (AD) → Death	[redacted]	Msm model using REGENCY IPD (see Appendix K)

AD, Active disease; CKD, Chronic kidney disease; CR, Complete response; IPD, Individual patient data; KOL, Key opinion leader; Msm, Multistate Model; PR, Partial response.

8.2.2 Transitions from CKD 4

Once patients have progressed to CKD Stage 4, they cannot return to CKD stages 1-3 because of the progressive and irreversible damage caused to the kidney tissues. Progression into CKD 4 indicates the patient has deteriorated and the future probabilities are only to remain in state CKD 4, progress further into CKD stage 5 or die.

Although the model enables the patients to move to response states within the CKD 4 state, no data was identified to be able to populate this section of the model. Therefore, the probabilities of moving to and in between *CKD 4 CR* and *CKD 4 PR* are set to 0% for all treatments. Considering that utilities in states 1-3b CR and PR are not substantially different, and further costs can be captured via rescue therapies, this simplification would likely amount to minimal impact on the results.

Sugrue et al., 2019 (86) performed a systematic literature review to inform the economic modelling of chronic kidney disease where an estimate of the annual transition rate from "CKD 4" to "CKD 5" of 0.067 is provided. This is used to inform the annual rate from *CKD_4_AD* to *CKD_5_D* where the 6 month transition probability can be calculated as $1 \quad \exp\left(\quad \frac{0.067}{2} \right) = 0.0329$

Sugrue et al. (86) is also used to inform the risk of death in CKD 4. Assuming that the transition probabilities from *CKD_4_AD*, *CKD_4_PR* and *CKD_4_CR* to death are all the same, 6-month transition probability from *CKD_4_AD*, *CKD_4_PR* and *CKD_4_CR* to death is calculated as $1 \quad \exp\left(\quad \frac{0.080}{2} \right) = 0.0392$

8.2.3 Transitions from CKD 5

Transitions from CKD 5 Dialysis toward CKD 5 Transplant were informed by TA882 (85) using the UK base case. In TA882, the company had assumed a 90% transplantation rate over two years. The EAG viewed this rate as being too high and amended the rate to 65% over two years, equivalent to 23.08% every 6 months, which is also used in this submission.

Sugrue et al 2019 (86) provide an estimate of the annual transition rate from "CKD 5 Transplant" to "CKD 5 Dialysis" of 0.082. Then, the 6-month transition probability from CKD_5_D to CKD_5_T can be calculated as $1 - \exp\left(-\frac{0.082}{2}\right) = 0.0402$

Similarly, Sugrue et al also provide annual transition rates from CKD 5 Dialysis and CKD 5 Transplant to Death which are 0.177 and 0.053 respectively. These are then also calculated into 6 months transitions probabilities as $1 - \exp\left(-\frac{0.177}{2}\right) = 0.0847$ and $1 - \exp\left(-\frac{0.053}{2}\right) = 0.0262$ respectively.

8.3 Modelling effects of subsequent treatments

N/R

8.4 Other assumptions regarding efficacy in the model

N/R

8.5 Overview of modelled average treatment length and time in model health state

Table 16 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Obi+MMF+PDS	N/A	N/A	N/A
MMF+PDS	N/A	N/A	N/A

MMF, Mycophenolate mofetil; Obi, obinutuzumab; PDS, Prednisone.

Table 17 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length Years	CKD_1_3b_AD	CKD_1_3b_PR	CKD_1_3b_CR	CKD_4_AD	CKD_4_PR	CKD_4_CR	CKD_5_D	CKD_5_T
Obi+MMF+PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMF+PDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AD, Active disease; CKD, Chronic kidney disease; CR, Complete response; MMF, Mycophenolate mofetil; Obi, obinutuzumab; PDS, Prednisone; PR, Partial response.

9. Safety

9.1 Safety data from the clinical documentation

The safety analysis is based on the safety-evaluable population in the REGENCY study comprising 268 patients - 136 patients in the obinutuzumab arm and 132 patients in the placebo arm, until the point of rescue. The safety-evaluable includes patients who received any part of a blinded infusion of obinutuzumab or placebo. Patients were grouped according to the treatment they actually received, regardless of the initial treatment arm they were assigned to during randomization (79).

The CCOD for the primary analysis was 15 August 2024. The overview of the safety findings from the Week 76 safety analysis is provided in Table 18 and key findings are summarized below the table.

Unless otherwise specified, safety data are presented in this section excluding AEs which occurred subsequent to receipt of rescue medication.

Overall, the safety results in REGENCY up to Week 76 indicate that obinutuzumab was generally well tolerated in patients with lupus nephritis. No new safety concerns were identified, and safety data up to Week 76 were overall consistent with the known safety profile of obinutuzumab and/or underlying disease of the patient population (79).

Table 18 Overview of safety events. REGENCY, safety evaluable population, CCOD 15 August 2024 (78, 79).

	Obinutuzumab (N=136)	Placebo (N=132)	Difference, % (95 % CI)
Number of adverse events, n	748	665	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	126 (92.6%)	117 (88.6%)	4.0 (-3.0, 11.0)
Number of serious adverse events*, n	68	35	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	44 (32.4%)	24 (18.2%)	14.2 (3.92, 24.42)
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	44 (32.4%)	22 (16.7%)	15.7 (5.6, 25.8)
Number of adverse reactions, n	[redacted]	[redacted]	N/A

	Obinutuzumab (N=136)	Placebo (N=132)	Difference, % (95 % CI)
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who had a dose reduction, n (%)	N/A, dose modification was not permitted	N/A, dose modification was not permitted	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	10 (7.4%)	5 (3.8%)	3.6 (-1.9, 9.0)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available. Applicant note: CTCAE v. 5.0 is used.

All adverse events

The incidence of patients who experienced at least one adverse event (AE) during the 76-week blinded treatment period was comparable in both arms (92.6% (n=126) in the obinutuzumab arm and 88.6% (n=117) in the placebo arm). The majority of AEs reported were non-serious ([redacted] of 748 AEs in the obinutuzumab arm vs [redacted] of 665 AEs in the placebo arm). Notable differences (≥5%) in AEs by System Organ Class (SOC) included:

- Infections and infestations: 72.1% (n=98) vs. 61.4% (n=81).
- Musculoskeletal and connective tissue disorders: [redacted]
- Injury, poisoning and procedural complications: [redacted] (78, 79).

Adverse events related to treatment

The proportion of patients who experienced at least one AE assessed by the investigator as related to blinded obinutuzumab or MMF was higher in the obinutuzumab arm ([redacted] n=84) compared with the placebo arm [redacted] The proportion of patients who experienced at least one AE assessed by the investigator as related to blinded obinutuzumab was higher in the obinutuzumab arm ([redacted] experiencing [redacted] events compared to the placebo arm ([redacted]) experiencing [redacted] events).

The most frequent AEs related to blinded obinutuzumab by system organ class (SOC) (≥10% of patients in either arm) were Infections and infestations ([redacted] and Injury, poisoning and procedural complications ([redacted]). Neutropenia was the only AE by preferred term (PT) with a ≥5% difference between the arms (7.4% [n=10] vs. 2.3% [n=3]) (78, 79).

Serious and fatal adverse events

The proportion of patients experiencing at least one serious adverse event (SAE) was higher in the obinutuzumab arm (32.4% [n=44]) compared with the placebo arm (18.2% [n=24]).

The most frequent serious adverse events observed among the obinutuzumab-treated patients were infections, including coronavirus disease 2019 (Covid-19)-related events, urinary tract infection, pneumonia, and gastroenteritis. As also seen in Table 19 below COVID-19 pneumonia is the only SAE with an incidence ≥ 5%.
Excluding COVID-19 SAEs, the imbalance remains but is less pronounced (27.2% [n=37] vs. 18.2% [n=24].

There were 3 deaths (2.2%), in the obinutuzumab arm (2 from COVID-19 pneumonia, 1 from nephrotic syndrome) and 1 death (0.8%) in the placebo arm (COVID-19). All fatal events except nephrotic syndrome were assessed as treatment-related. One additional death (B-cell Lymphoma) occurred in the placebo arm after the data cut but with onset during the 76-week treatment period.

Excluding fatalities and one SAE of weight loss, all SAEs in the patients who received obinutuzumab had resolved or were resolving by week 76 (78, 79).

Table 19 Serious adverse events above ≥ 5%, REGENCY, safety evaluable population, CCOD 15 August 2024 (78, 79)

Adverse events	Obinutuzumab (N=136)		Placebo (N=132)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
COVID-19 pneumonia	7 (5.1%)	[redacted]	0	0

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Serious adverse events related to treatment

Overall, a higher proportion of patients experienced at least one SAE that was assessed by the investigator as related to blinded obinutuzumab in the obinutuzumab arm [redacted] compared with the placebo arm ([redacted]

The most frequent SAEs by SOC (≥2% in either arm) that were assessed by the investigator as related to blinded obinutuzumab were:

- Infections and infestations ([redacted]
- Blood and lymphatic system disorders [redacted]

The most frequent SAEs by PT (≥2% in either arm) that were assessed by the investigator as related to blinded obinutuzumab were:

[redacted]COVID-19 pneumonia ([redacted]
- Neutropenia ([redacted] (78, 79).

Grade 3-5 adverse events

Grade 3–5 AEs were reported in 32.4% (n=44) of the patients in the obinutuzumab arm versus 16.7% (n=22) in the placebo arm. The difference was driven by infections, mainly COVID-19 infections as described previously.

Grade 3-5 AEs by SOC with notable differences (≥5 % between arms) were:
- Infections and infestations: [redacted]
- Blood and lymphatic system disorders[redacted]).

Grade 3-5 AEs by PT with notable differences were:
- COVID-19 pneumonia: [redacted]%.
- Neutropenia: [redacted](78, 79).

Adverse events leading to dose modification or discontinuation

Study protocol prohibited obinutuzumab dose modifications but allowed for infusion rate adjustment for IRRs or dose interruption. Dose interruptions due to SAEs were infrequent across both arms ([redacted] in the obinutuzumab arm vs[redacted] in the placebo arm). Dose modifications for MMF were allowed and a higher proportion of patients experienced at least one AE leading to dose modification/interruption of blinded obinutuzumab or MMF in the obinutuzumab [redacted]) compared to the placebo arm ([redacted]. Of these, [redacted]) in the obinutuzumab arm and [redacted]) in the placebo arm experienced at least one AE leading to dose interruption of blinded obinutuzumab alone. The difference in the proportion of patients with AEs leading to dose modification/interruption of blinded obinutuzumab or MMF versus interruption of blinded obinutuzumab alone suggests that the majority of AEs led to dose modification or interruption of MMF and not blinded obinutuzumab.

The most frequent AEs by PT (≥2% of patients in either arm) that led to dose interruption of blinded obinutuzumab were COVID-19 (0.7% [n=1] vs. 3.8% [n=5] and infusion related reactions (5.1% [n=7] vs. 0.8% [n=1]). In addition, there was a notable difference (≥5% difference between arms) in the SOC Injury, poisoning and procedural complications, which was driven by infusion-related reactions.

The proportion of patients with at least one AE leading to discontinuation from blinded obinutuzumab treatment was low in both arms (7.4% [n=10] in the obinutuzumab arm vs. 3.8% [n=5] in the placebo arm). The most frequent AEs by SOC (≥2% of patients in either arm) resulting in obinutuzumab discontinuation were:
- Infections and infestations: 3.7% (n=5) vs. 1.5% (n=2)
- Blood and lymphatic system disorders: 2.2% (n=3) vs. 0% (78, 79).

Adverse events of special interest

Adverse events of special interest (AESIs) included infusion-related reactions (IRR): Grade 3-5 infections, hepatitis B reactivation, progressive multifocal leukoencephalopathy, drug-related neutropenia, drug-related thrombocytopenia, gastrointestinal perforation

and worsening of pre-existing cardiac conditions. AESIs for obinutuzumab were generally balanced between treatment arms, with the exception of AESI categories of IRRs, Grade 3-5 infections, and drug-related neutropenia.

Infusion-related reactions
IRR is an expected risk with obinutuzumab. In the REGENCY study, the proportion of patients who experienced at least one AESI of IRRs was 15.4% (n=21) in the obinutuzumab arm vs. 11.4% (n=15) in the placebo arm. Incidence and severity was highest at the first infusion and showed a decreasing trend with additional infusions.

The majority of IRRs in the obinutuzumab arm were Grade 1–2 (14.0% [n=19**]**) and resolved with protocol-guided management. Grade 3-5 IRRs occurred only in the obinutuzumab arm (1.5% [n=2]) following the first infusion; 1 patient had a non-serious Grade 3 IRR, and 1 patient had a serious Grade 4 IRR; both events resolved. The Grade 4 IRR was assessed as related to blinded obinutuzumab and led to discontinuation of obinutuzumab. There were no reports of Grade 5 IRRs in patients in the obinutuzumab arm.

The most frequent IRRs (≥2% in either arm) were balanced between arms:
- Nausea (4 patients [2.9%] vs. 4 patients [3.0%]).
- Headache (4 patients [2.9%] vs. 3 patients [2.3%]).
- Vomiting (4 patients [2.9%] vs. 2 patients [1.5%]).

Grade 3-5 infections
Grade 3–5 infections are an expected risk for obinutuzumab and occurred in 15.4% (n=21) of patients in the obinutuzumab arm vs. 6.8% (n=9) in the placebo arm. While the incidence was higher with obinutuzumab, the imbalance was primarily driven by COVID-19-related events. Excluding COVID-19 AEs, the difference between arms was less pronounced: 11.0% (n=15) vs. 6.8% (n=9), respectively.

The most frequent Grade 3-5 infections by PT (≥2% of patients in either arm) were:
- COVID-19 pneumonia (6 patients [4.4%] and 0 patients)
- Urinary tract infection (5 patients [3.7%] and 3 patients [2.3%])
- Gastroenteritis (4 patients [2.9%] and 3 patients [2.3%])
- COVID-19 (4 patients [2.9%] and 1 patient [0.8%])
- Pneumonia (2 patients [1.5%] and 3 patients [2.3%])

Grade 3–5 infections led to treatment discontinuation in 2.2% (n=3) of the patients in the obinutuzumab arm and 0% in the placebo arm. As described previously Grade 5 (fatal) infections were reported in 2 patients in the obinutuzumab arm (COVID-19 pneumonia) and 1 patient in the placebo arm (COVID-19). Excluding the fatal cases, all Grade 3–5 infections resolved.

Drug-related neutropenia
Drug-related neutropenia is an expected risk for obinutuzumab and the proportion of patients who experienced at least one AESI of drug-related neutropenia was higher in the obinutuzumab arm (12.5% [n=17]) compared with the placebo arm (3.8% [n=5]).

Five patients in the obinutuzumab arm experienced events that were considered serious, including the 1 patient with a Grade 4 serious febrile neutropenia. All events of serious drug-related neutropenia were assessed as related to blinded obinutuzumab and resolved with treatment per protocol guidance, including 1 patient who experienced Grade 4 drug-related neutropenia which recovered with sequelae (no further information available). Drug-related neutropenia led to interruption of blinded obinutuzumab in 1 patient, and led to discontinuation of blinded obinutuzumab in 2 patients (febrile neutropenia and neutropenia [1 patient each]) (78, 79).

Adverse events by obinutuzumab regime

Analysis of safety events by obinutuzumab regimen showed that the number of patients experiencing at least one AE up to Week 76 was comparable across the 2-2-2 and 2-2-1 obinutuzumab regimens ([redacted] in 2-2-2 vs. [redacted] in 2-2-1). However, the proportion of patients experiencing SAEs, serious infections, Grade 3–5 AEs, AEs with fatal outcome, as well as the majority of AESIs was higher in the 2-2-1 regimen. An analysis of AEs reported in the obinutuzumab arm up to Week 50 showed that a difference between these two groups of patients already existed prior to Week 50, when there was no difference in the dosing schedule between groups. This suggests that the higher number of events in patients randomized to the 2-2-1 regimen compared with the 2-2-2 regimen up to Week 76 was not driven by the absence or presence of an additional dose at Week 50 (78, 79).

Adverse events used in the health economic model

To estimate cost associated with the treatment of adverse events frequencies observed in REGENCY were used for Obi+MMF+PDS and MMF+PDS respectively. The model includes costs for adverse event that occurred in >1% of patients in either arm.

Table 20 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm

Adverse events	Intervention	Comparator		
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm
[redacted]	[redacted]	[redacted]	REGENCY	>1% of patients in arm

9.2 Safety data from external literature applied in the health economic model

N/R

Table 21 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n								

10. Documentation of health-related quality of life (HRQoL)

Table 22 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	REGENCY	Clinical effectiveness and utility

10.1 Presentation of the health-related quality of life [make a subsection for each of the applied HRQoL instruments]

10.1.1 Study design and measuring instrument

The REGENCY study design is described in Section 6.1.1. The EQ-5D-5L was an exploratory endpoint used to assess health status utility scores in patients treated with obinutuzumab or placebo to support health economic modeling.

The EQ-5D-5L is a validated, self-reported health status questionnaire designed to generate health utility scores for use in health economic analyses (94-97). It consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The health utility index is scored from 0 to 1, while the Visual Analog Scale (VAS) component measures the patient's current health state on a scale from 0 (worst imaginable) to 100 (best imaginable).

10.1.2 Data collection

Health-related quality of life (EQ-5D-5L) was assessed via the self-administered instrument at the clinical site at baseline and at Weeks 24, 50, and 76. Data was collected in the Efficacy-Evaluable population. Assessments were completed prior to the patient receiving information on disease status and prior to the performance of non-PRO assessments or study treatment administration, unless otherwise specified.

Following completion, site personnel performed a review, requesting that patients clarify ambiguous markings or confirm intentionally blank items. Completion rates for HRQoL assessments remained high (90% or above) throughout the blinded treatment period (91) (Table 23 and Table 24).

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Table 23 Pattern of missing data and completion, EQ-5D-5L utility index scores, Efficacy-Evaluable Patients

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
		Obinutuzumab		
Baseline	135	[redacted]	[redacted]	[redacted]
Week 24	135	[redacted]	[redacted]	[redacted]
Week 50	135	[redacted]	[redacted]	[redacted]
Week 76	135	[redacted]	[redacted]	[redacted]
		Placebo		
Baseline	136	[redacted]	[redacted]	[redacted]
Week 24	136	[redacted]	[redacted]	[redacted]
Week 50	136	[redacted]	[redacted]	[redacted]
Week 76	136	[redacted]	[redacted]	[redacted]

Table 24 Pattern of missing data and completion, EQ-5D-5L VAS scores, Efficacy-Evaluable Patients

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
		Obinutuzumab		

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	135	[redacted]	[redacted]	[redacted]
Week 24	135	[redacted]	[redacted]	[redacted]
Week 50	135	[redacted]	[redacted]	[redacted]
Week 76	135	[redacted]	[redacted]	[redacted]
		Placebo		
Baseline	136	[redacted]	[redacted]	[redacted]
Week 24	136	[redacted]	[redacted]	[redacted]
Week 50	136	[redacted]	[redacted]	[redacted]
Week 76	136	[redacted]	[redacted]	[redacted]

10.1.3 HRQoL results

EQ-5D-5L utility index scores

EQ-5D-5L health states from REGENCY have been converted to the Danish population using Danish preference weights for EQ-5D-5L. Estimates are derived from an analysis based on a mixed-effect model of repeated measures (MMRM) using an unstructured covariance matrix: Value at Visit = Baseline + Week + Treatment + Treatment*Week (repeated values over Week) (91).

The MMRM analysis includes only patients with an assessment at baseline and at least one post-baseline value, ensuring statistical robustness. Consequently, the analysis population (N) is slightly smaller than the total number of patients who completed the questionnaire at specific visits, as the model excludes cases with missing baseline data or assessments that occurred at discontinuation visits (91).

Baseline EQ-5D-5L utility index scores were comparable between the treatment arms, with a mean (SE) of [redacted] for the obinutuzumab arm and [redacted] for the placebo arm (

Table 25). Analysis of the change from baseline indicates no significant difference in change from baseline by visit in either arm (Figure 5) (91).

Descriptive statistics show that the mean in EQ-5D-5L utility index score at Week 24, 50, and 76 in the obinutuzumab arm were comparable to the placebo arm. By Week 76, the mean difference between treatments was [redacted] (

Table 25) (91).

[redacted]

Figure 5 Change from baseline by visit, EQ-5D-5L utility index scores, Efficacy–Evaluable Population: CCOD, 15 August 2024

Table 25 HRQoL summary statistics, EQ-5D-5L utility index scores, MMRM analysis: Efficacy–Evaluable population: CCOD 15 August 2024

	Intervention Obinutuzumab		Comparator Placebo		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]				
Week 24	[redacted]				
Week 50	[redacted]				
Week 76	[redacted]				

EQ-5D-5L VAS

Descriptive statistics at baseline include only patients with an assessment at baseline and at least one post-baseline value. Estimates are derived from an analysis based on a mixed-effect model of repeated measures (MMRM) using an unstructured covariance matrix: Value at Visit = Baseline + Week + Treatment + Treatment*Week (repeated values over Week). Similar to the utility index, the MMRM analysis population (N) is slightly smaller than the total number of patients who completed the questionnaire at specific visits to ensure statistical robustness by requiring paired baseline and post-baseline data (91).

Baseline EQ-5D-5L VAS scores were comparable between the treatment arms, with a mean (SE) of [redacted] for the obinutuzumab arm and [redacted]) for the placebo arm (Table 26). Analysis of the change from baseline indicates no significant difference in change from baseline by visit in either arm (Figure 6) (91).

Descriptive statistics indicate that the mean in EQ-5D-5L VAS scores at Week 24, 50, and 76 in the obinutuzumab arm were comparable to the placebo arm. By Week 76, the mean difference between treatments was 2.331 (95% CI: -2.17, 6.83; p = 0.309) (Table 26) (91).

[redacted]

Figure 6 Change from baseline by visit, EQ VAS scores, Efficacy–Evaluable population: CCOD, 15 August 2024

Table 26 HRQoL summary statistics, EQ VAS, MMRM analysis: Efficacy–Evaluable population: CCOD, 15 August 2024

	Intervention Obinutuzumab		Comparator Placebo		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]				
Week 24	[redacted]				
Week 50	[redacted]				
Week 76	[redacted]				

10.2 Health state utility values (HSUVs) used in the health economic model

Health state utility values were estimated based on REGENCY data where EQ-5D-5L data were collected along with external literature that were used to inform subsequent health stated not captured in the REGENCY trial.

10.2.1 HSUV calculation

Data from REGENCY were used to inform HSUVs within the health states *CKD_1_3B_AD, CKD_1_3b_PR* and *CKD_1_3b_CR* using Danish weights from Jensen et al. (2021) (98). [redacted]

[redacted]

10.2.1.1 Mapping

N/R given that EQ-5D-5L was collected in the trial

10.2.2 Disutility calculation

N/R as HSUVs are collected for both the intervention and the comparator and therefore assumed to account for the impact of adverse events on HRQoL

10.2.3 HSUV results

Table 27 reports HSUVs estimated from REGENCY. In the base case, separate utility values per trial arm are used but the model included an option to use utility data from a pooled analysis, i.e. same utility values irrespective of treatment received. [redacted]

[redacted]

Table 27 Overview of health state utility values from REGENCY

	Results [95% CI]	Number of Observation	Instrument	Tariff (value set) used	Comments
HSUVs from REGENCY - per treatment arm					
CKD_1_3B_AD Obinutuzumab	[redacted]	[redacted]	EQ-5D-5L	DK	Used in base case
CKD1-3b_AD MMF	[redacted]	[redacted]	EQ-5D-5L	DK	Used in base case
CKD_1_3B_PR	[redacted]	[redacted]	EQ-5D-5L	DK	Used in base case

	Results [95% CI]	Number of Observation	Instrument	Tariff (value set) used	Comments
Obinutuzumab					
CKD_1_3B_PR MMF	[redacted]	[redacted]	EQ-5D-5L	DK	Used in base case
CKD_1_3B_CR Obinutuzumab	[redacted]	[redacted]	EQ-5D-5L	DK	Used in base case
CKD_1_3B_CR MMF	[redacted]	[redacted]	EQ-5D-5L	DK	Used in base case
HSUVs from REGENCY - pooled analysis					
CKD_1_3B_AD	[redacted]	[redacted]	EQ-5D-5L	DK	
CKD_1_3B_PR	[redacted]	[redacted]	EQ-5D-5L	DK	
CKD_1_3B_CR	[redacted]	[redacted]	EQ-5D-5L	DK	

AD, Active disease; CI, Confidence Interval; CKD, Chronic kidney disease; CR, Complete response; EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; HSUV, Health state utility values; MMF, mycophenolate mofetil; PR, Partial response.

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

For a number of health states in the model, external data was utilized, as relevant data was not available from REGENCY. HSUVS used in the model from external literature sources can be found in Table 29. Two external sources are used to inform HSUVs within our model. Jesky et al 2016 (99), identified via TA882, are used for the CKD 4 health states. The study presented EQ-5D-3L data from the British *Renal Impairment In Secondary Care (RIISC) study* which consisted of 745 patients with pre-dialysis CKD who were considered to be at high risk of progressing to ESKD.

HSUVs in CKD 5 health states were sourced from DMCs assessment of imlifidase (100) where Eriksson et al 2017 (87) were used. The study by Eriksson et al investigated quality of life among patients across all stages of autosomal dominant polycystic kidney disease in the Nordics, including Danish patients who are in dialysis or who have received a kidney transplant.

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

Table 28 Overview of health state utility values [and disutilities]

Table 29 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
CKD 4 AD	0.655 [N/A]	EQ-5D-3L	UK	TA882 Submission, which used Jesky et al. (99) Utilities were calculated by applying estimated decrement from Jesky et al to the UK utilities from REGENCY
CKD 4 CR	0.775 [N/A]			
CKD 4 PR	0.745 [N/A]			
CKD 5 Dialysis	0.73 [0.68 -0.79]	EQ-5D-3L	DK	DMCs assessment of Imlifidase
CKD 5 Transplant	0.85 [0.81 -0.89]			

AD, Active disease; CI, Confidence Interval; CKD, Chronic kidney disease; CR, Complete response; N/A, Not applicable; PR, Partial response.

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

The dosage for the pharmaceuticals included in the health economic analysis can be found in Table 30.

The model does not contain an option to choose between vial sharing as methylprednisolone (MPDL) is the only IV treatment that is administered weight based. Due to the low price of this pharmaceutical, and the fact that it is administered in both treatment arms, this simplifying assumption was considered to have minimal effect on the results.

Treatment duration can be selected from the "Model Inputs" sheet and is measured in model cycles (i.e. 6 months). The user can select between 3, 6, 12 or 18 cycles, which means that treatment duration can be set to 1.5, 3, 6 or 9 years. In the base-case, a 36-month treatment duration is applied for all treatments in accordance with the REGENCY protocol (which suggests that responders should continue treatment on 6-monthly maintenance) and aligned as well to TA882. However, there is uncertainty surrounding this assumption, as patients who respond would be expected to continue on treatment, and others who do not respond may stop treatment before 36 months. According to 2025 EULAR guidelines (101), it is also suggested that following renal response, treatment (immunosuppressive and/or biologic therapy) should generally continue for at least 3 years. In an ad-board held in the UK, most advisors agreed that if a stopping rule were to be used, it would need to be based on B cell depletion and there is reason to continue dosing a patient who has low B cell counts. These advisors agreed that they would make B cell depletion the focus of treatment. There was, however, not a clear consensus with regards to when the treatment should be stopped, stating that they preferred to have flexibility to make a case-by-case decision. Some advisors stated they would base treatment decisions on the REGENCY data (18 months treatment).

Usage of prednisone and methylprednisolone in REGENCY differed slightly from Danish clinical practice which has been adjusted with input from the Danish clinician consulted in connection with the development of this dossier (the user can choose to use dosage from REGENCY in the sheet "Cost inputs"). The changes only affect the cost side of the health economic model. Dosage of mycophenolate in REGENCY was deemed sufficiently aligned with Danish clinical practice and as such used in the model.

Table 30 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Obinutuzumab	1000 mg	100%	On weeks 1, 3, 25, 27 and 53. Subsequent infusions every 6 months starting at Week 80	N/R
Mycophenolate Mofetil	2.5 g per day	100%	Schedule & dosing: REGENCY	N/R

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Methylprednisolone	IV: 1000 mg prior to or at screening plus 80 mg prior to every study treatment infusion	100%	Schedule & dosing: Danish clinical practice	N/R
Prednisone	Oral: 0.5 mg/kg/day (maximum 60 mg/day) until week 24, 5 mg/day thereafter	100%	Schedule & dosing: Danish clinical practice	N/R

N/R, Not relevant

11.2 Medicines– co-administration

The model includes costs associated with rescue treatment which constitutes treatments needed when patients do not respond sufficiently on either Obi+MMF+PDS or MMF+PDS. Share of patients who need rescue treatment in the respective arm is based on REGENCY and costs are incurred as a lump sum (i.e. not upon entering a given health state). In REGENCY, [redacted] and [redacted] of patients received rescue therapy for the intervention arm and comparator arm respectively.

The Danish clinical expert consulted advised that the majority of patients in need of rescue therapy will receive cyclophosphamide potentially in combination with belimumab. Based on this input it is assumed that all patients who receive rescue therapy are treated with six cycles of cyclophosphamide IV (500 mg) and that 20% of the relevant patients also receive belimumab for three months (400 mg pr week for 4 weeks followed by 200 mg pr. Week).

11.3 Administration costs

Administration costs were included in connection with the administration of IV treatments. The DRG code used can be found in Table 31.

Table 31 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion	See Table 30	1,684	08MA98	DRG 2025

11.4 Disease management costs

Disease management cost is health state dependent irrespective of treatment received. Frequencies were sourced from NICEs assessment of Voclosporin (85). Costs were

estimated based on Danish DRGs, Labportal and published literature estimates mainly identified via the submitted dossier for the DMCs assessment of Voclosporin (102). Frequencies from the NICE assessment of Voclosporin were sanity checked against input which the applicant of the submitted dossier for the DMCs assessment of Voclosporin received from Danish clinicians (input identified from section 8.5.1 of the submitted dossier for Voclosporin to the DMC). The frequencies from NICEs assessment of Voclosporin was deemed as sufficiently in accordance with Danish clinical practice.

The model distinguishes between one-off costs and recurrent costs. One-off costs constitute costs that are incurred upon patients entering a given health state whereas recurrent costs are cost that are incurred for patients remaining in a given health state at the end of a given cycle.

Table 32 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	Reference
Nurse visit	See appendix	1,578	DRG 2025 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år. Source Interactive DRG
Specialist visit	See appendix	1,578	DRG 2025 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år. Based on Voclosporin submission to DMC
Kidney biopsy	See appendix	5,879	DRG 2025 09PR04: Biopsi og væskeudsugning, overfladisk. Source: Interactive DRG
Urinalysis (includes eGFR, serum albumin, proteinuria and urinary sediment)	See appendix	122	Labportal: NPU09102 (creatinin [GFR]), NPU19677(Albumin), NPU03958 (protein;U), Internal prices. Based on Voclosporin submission to DMC
Complete blood count	See appendix	46	Labportal: NPU17580 (Leukocytetypes), NPU02902 (neutrofilocytes), and NPU02319 (Haemaglobin + thrombocytes). Based on Voclosporin submission to DMC
Serum immunoglobulin measurement	See appendix	87	Labportal: NPU19795 (IgA), NPU19814 (IgG), NPU19825 (IgM). Based on Voclosporin submission to DMC
Chronic infection screening	See appendix	31	Labportal: NPU19748 (C-reaktivt protein [CRP];P), and NPU04100 (B-Leukocyttype; antalk.)

Activity	Frequency	Unit cost [DKK]	Reference
			internal prices. Based on Voclosporin submission to DMC
Cholesterol and lipid monitoring	See appendix	91	Labportal: NPU01568 (LDL cholesterol), NPU01569 (VLDL), and NPU01567 (HDL). Internal prices. Based on Voclosporin submission to DMC
Anti-dsDNA and C3 and C4 level monitoring	See appendix	619	Labportal: NPU16393 DNA(dobbeltstrenget)-antistof(IgG);P, NPU19740 Complement C3;P, NPU19742 Complement C4;P. Based on Voclosporin submission to DMC
Dialysis	See appendix	198,206	Based on Voclosporin submission to DMC which used: Samfundsøkonomisk gevinst ved nyretransplantation - DAMVAD Analytics for 7LIV, 2017 (103)
Initial assessment for kidney transplant	See appendix	1,511	DRG 11 MA98. Based on Voclosporin submission to DMC
Waiting list clinic attendance (pre-transplant)	See appendix	1,511	DRG 11 MA98. Based on Voclosporin submission to DMC
Kidney transplantation	See appendix	256,598	11MP02
Post-kidney transplantation, year 1	See appendix	78,412	Based on DMC assesment of Voclosporin which used: Samfundsøkonomisk gevinst ved nyretransplantation - DAMVAD Analytics for 7LIV, 2017 (103)
Post-kidney transplantation, year 2+	See appendix	37,471	Based on DMC assesment of Voclosporin which used: Samfundsøkonomisk gevinst ved nyretransplantation - DAMVAD Analytics for 7LIV, 2017 (103)
Vitamin D supplements	See appendix	3,630	Based on Voclosporin submission to DMC
ESAs and EPO	See appendix	1,757	Based on Voclosporin submission to DMC

Activity	Frequency	Unit cost [DKK]	Reference
Phosphate binders	See appendix	705	Based on Voclosporin submission to DMC
ACEI or ARB	See appendix	248	Based on Voclosporin submission to DMC
Anti-hypertensive medication	See appendix	248	Based on Voclosporin submission to DMC
Ultrasound	See appendix	1,595	DRG 2025 30PR11: UL scanning, ukompliceret. Based on Voclosporin submission to DMC
Echocardiogram	See appendix	2,111	DRG 2025 30PR11: Kardiologisk undersøgelse, udvidet. Based on Voclosporin submission to DMC

11.5 Costs associated with management of adverse events

The health economic analysis included cost for adverse events that were considered to be associated with additional costs to the health care sector, and which were observed in >1% of either the intervention or comparator arm. Costs were estimated by use of DRG tariffs. The costs are not accrued over time but occur in the initial cycle of the model.

Table 33 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff (DKK)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	DRG code	Unit cost/DRG tariff (DKK)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

11.6 Subsequent treatment costs

N/R as rescue treatment is described in section 11.2.

Table 34 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/R	N/R	N/R	N/R	N/R

N/R, Not relevant.

11.7 Patient costs

Patient costs and transportation time were included in the model using the rates provided by the DMC Methods handbook (203 DKK pr. hour and 3.73 DKK pr. km)

In the submitted model, every health state is associated with a given amount of patient time pr. cycle. Time spent in each health state was sourced from the Voclosporin submission to the DMC (102), where the applicant had estimated patient time in each state through interviews with Danish physicians treating LN patients. Hours spent pr. cycle in each state are presented in Table 35.

It was not assumed that patients would travel in connection with all resource items described in section 11.4,. Patients are only assumed to have travel cost in association with nurse visits, specialist visits, kidney biopsy, dialysis and kidney transplantation. The

remaining costs described in section 11.4 are assumed to occur in connection with these visits.

Table 35 Patient costs used in the model

Activity	Time spent [hours]
CKD_1_3b_AD	12
CKD_1_3b_PR	8.25
CKD_1_3b_CR	3.75
CKD_4_AD	12
CKD_4_PR	8.25
CKD_4_CR	3.75
CKD_5_D	315
CKD_5_T	15

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/R

12. Results

12.1 Base case overview

Table 36 Base case overview

Feature	Description
Comparator	MMF
Type of model	De novo cohort multi state Markov model
Time horizon	90 years (life time)
Treatment line	1st line
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in REGENCY. Danish population weights were used to estimate health-state utility values along with external literature to inform HSUVs in health states not available from REGENCY

Feature	Description
Costs included	Medicine costs, administration costs, disease management cost, cost of adverse events and patient cost.
Average time on treatment	Intervention: [redacted] years Comparator: [redacted] years
Inclusion of waste	Not included
Average time in model health state	See Excel model under sheet "Markov Model" cells K6-T9

EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; MMF, Mycophenolate mofetil

12.1.1 Base case results

Table 37 Base case results, discounted estimates

	Obi+MMF+PDS	Obi+MMF+PDS	Difference
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Supportive Care Costs	[redacted]	[redacted]	[redacted]
Rescue therapy	[redacted]	[redacted]	[redacted]
Patient time and transport costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life-years gained In CKD_1_3b_AD	[redacted]	[redacted]	[redacted]
Life-years gained In CKD_1_3b_PR	[redacted]	[redacted]	[redacted]
Life-years gained In CKD_1_3b_CR	[redacted]	[redacted]	[redacted]
Life-years gained In CKD_4_AD	[redacted]	[redacted]	[redacted]
Life-years gained In CKD_4_PR	[redacted]	[redacted]	[redacted]
Life-years gained In CKD_4_CR	[redacted]	[redacted]	[redacted]

	Obi+MMF+PDS	Obi+MMF+PDS	Difference
Life years gained In CKD_5_D	[redacted]	[redacted]	[redacted]
Life-years gained In CKD_5_T	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
Life years gained In CKD_1_3b_AD	[redacted]	[redacted]	[redacted]
Life-years gained In CKD_1_3b_PR	[redacted]	[redacted]	[redacted]
Life-years gained In CKD_1_3b_CR	[redacted]	[redacted]	[redacted]
Life years gained In CKD_4_AD	[redacted]	[redacted]	[redacted]
Life years gained In CKD_4_PR	[redacted]	[redacted]	[redacted]
Life-years gained In CKD_4_CR	[redacted]	[redacted]	[redacted]
Life years gained In CKD_5_D	[redacted]	[redacted]	[redacted]
Life years gained In CKD_5_T	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Scenario analysis of parameters associated with uncertainty are shown in Table 38.

Table 38 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	[redacted]	[redacted]
Treatment duration	Average treatment duration changed to 3 cycles	Uncertainty about actual treatment length	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Treatment duration	Average treatment duration changed to 12 cycles	Uncertainty about actual treatment length	[redacted]	[redacted]	[redacted]
Treatment effect waning	Waning is assumed (decrease starting at cycle 10 and is null at cycle 20)	Uncertainty about occurrence of waning in clinical practice	[redacted]	[redacted]	[redacted]

12.2.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was conducted. PSA allows the computation of expected values of a model's results and assessing the uncertainty around these expected values when input variables are uncertain. The assessment of expected values and measures of uncertainty is done using simulation with all input variables that are subject to uncertainty being varied randomly according to their observed distribution. Table 39 provides an overview of the assumed distributions for the various parameters. The standard error (SE) associated with the parameter were used to define parameter uncertainty if available. The PSA was run with a 1000 iterations. Further information is provided in Appendix G

Table 39. Distributions used in the probabilistic sensitivity analysis

Type	Parameter	Distribution
Efficacy	Transition Probabilities	Dirichlet
	Adverse event rates	Log normal
Costs	Supportive care cost	Log normal
	Administration cost	Log normal
	Adverse event cost	Log normal
Utilities	Health state	Beta
	Number of adverse events observed in the trial	Log normal

Figure 7. Cost-effectiveness plane in terms of incremental costs and QALYs

Figure 8. Cost-effectiveness acceptability curve

Figure 9. Convergence Plot

13. Budget impact analysis

Table 40 report estimated number of new patients treated each year in the event of a recommendation by the DMC based on the assumptions described in section 3.2.

Table 41 report the resulting budget impact analysis.

Table 40 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Obi+MMF+PDS	17	17	17	17	17
MMF+PDS	0	0	0	0	0
			Non-recommendation		
Obi+MMF+PDS	0	0	0	0	0
MMF+PDS	17	17	17	17	17

MMF. Mycophenolate mofetil; Obi. obinutuzumab; PDS. Prednisone

Table 41 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

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Appendix A. Main characteristics of studies included

Table 42 Main characteristic of studies included

Trial name: REGENCY (Study CA41705)	NCT number: NCT04221477
Objective	To evaluate the efficacy and safety of obinutuzumab in patients with ISN/RPS 2003 Class III or IV, with or without concomitant Class V, lupus nephritis treated with standard-of-care therapy consisting of MMF and glucocorticoids,
Publications – title, author, journal, year	Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis, Furie RA, Rovin BH, Garg JP et al,, N Engl J Med, 2025
Study type and design	Phase III, randomized, double-blind, placebo-controlled, multicentre, parallel-group study, Patients were randomized 1:1 to obinutuzumab or placebo, Obinutuzumab patients were further randomized 1:1 to one of two dosing regimens (2-2-2 or 2-2-1), Status: Ongoing (primary analysis completed, estimated completion 2031),
Sample size (n)	271 randomized patients (Obinutuzumab: 135; Placebo: 136),
Main inclusion criteria	Adults 18–75 years; active or active/chronic ISN/RPS 2003 Class III or IV proliferative lupus nephritis (with or without Class V); UPCR ≥ 1 g/g on a 24-hour collection,
Main exclusion criteria	Pregnancy/breastfeeding; severe renal impairment (eGFR < 30 mL/min/1,73m² or ESKD requiring dialysis/transplant); recent receipt of excluded therapies (e,g,, anti-CD20 within 9 months, cyclophosphamide within 2 months); known active or major infection
Intervention	Obinutuzumab 1000 mg intravenous infusion, Dosing schedule: Day 1, Weeks 2, 24, 26, 50*, and 52 (*Week 50 omitted in the 2-2-1 regimen), Patients: 135 randomized (69 to 2-2-2 regimen; 66 to 2-2-1 regimen), All received background MMF and glucocorticoids
Comparator(s)	Placebo intravenous infusions on the same schedule as obinutuzumab (Day 1, Weeks 2, 24, 26, 50, and 52), Patients: 136 randomized, All received background SoC (MMF titrated to 2,0–2,5 g/day and glucocorticoids),
Follow-up time	Primary analysis at Week 76, Blinded treatment continues for adequate responders post-Week 76 (e,g,, visits up to Week 184 reported in exploratory data), All patients enter follow-up for at least 12 months after the last dose

Trial name: REGENCY (Study CA41705)	NCT number: NCT04221477
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	[State all primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application, Definition of included outcomes and results must be provided in Appendix D,] **Endpoints included in this application:** The primary endpoint was the proportion of patients achieving Complete Renal Response (CRR) at Week 76, Secondary endpoints were CRR with successful prednisone taper (Week 76); Proteinuric response (Week 76); Mean change in eGFR (Baseline to Week 76); Death or renal-related events (through Week 76); ORR at Week 50; Change in FACIT-F (Baseline to Week 76), and safety, Exploratory endpoints were health-related quality of life (HRQoL) as assessed by EQ-5D,5L and Time to LN flare, **Other endpoints:** Change in anti-dsDNA and C3 (Week 50); Change in SLEDAI-2K (Week 76); Time to onset of CRR; Time to unfavourable kidney outcome were included as exploratory endpoints in the study, but results are not included in this application,
Method of analysis	Efficacy-evaluable population (all randomized patients grouped by assigned treatment), Primary analysis used a Cochran-Mantel-Haenszel test, stratified by region and race, with multiple imputation for missing data, Time-to-event outcomes analysed via Kaplan-Meier plots and stratified log-rank tests,
Subgroup analyses	Pre-specified: Subgroups based on sex, race, region, baseline UPCR (<3 vs ≥3 mg/mg), anti-dsDNA (≤120 vs >120 kU/L), C3, C4, biopsy class, and prior LN history, Analysis: Exploratory forest plots of difference in proportion of CRR at Week 76, Results generally showed consistent benefit across high disease activity subgroups
Other relevant information	REGENCY repeat biopsy data (expected Q4 2025) will assess histologic activity in clinically stable patients, The trial was conducted during the COVID-19 pandemic, which influenced the rate of serious infection adverse events,

Appendix B. Efficacy results per study

Results per study

Table 43 Results per study, REGENCY (NCT04221477)

Results of REGENCY (NCT04221477)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95 % CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
CRR at Week 76	Obi	135	46,4% (37,95, 54,86)	13,4%	1,95, 24,84	0,0232	N/A	N/A	N/A	The proportion of responders in the obinutuzumab and placebo arms were compared using the Cochran–Mantel–Haenszel (CMH) test, stratified by region and race, Statistical testing was conducted at two-sided 5% significance level, The proportion of patients achieving CRR is presented for each treatment arm along with the adjusted difference, 95% CI for the adjusted difference, and p-value, Missing data were imputed using multiple imputation (fully conditional specification predicted mean matching method), Prior to	REGENCY (79)
	Placebo	136	33,1% (25,18, 41,00)								

Results of REGENCY (NCT04221477)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95 % CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										multiple imputation, missing 24-hour UPCR was first imputed by spot UPCR,	
CRR with successful prednisone taper at Week 76	Obi	135	42,7% (34,32, 51,09)	11,9%	0,57, 23,18	0,0421	N/A	N/A	N/A	CMH test stratified by region and race, Missing values were handled via multiple imputation (FCS predicted mean matching),	REGENCY (79)
	Placebo	136	30,9% (23,12, 38,65)								
Proteinuric response at Week 76	Obi	135	55,5% (47,09, 63,95)	13,7%	2,01, 25,36	0,0227	N/A	N/A	N/A	CMH test stratified by region and race, Missing values were handled via multiple imputation (FCS predicted mean matching),	REGENCY (79)
	Placebo	136	41,9% (33,62, 50,20)								
Mean change in eGFR from baseline to Week 76	Obi	135	2,3 mL/min/1,73 m² (SE: 2,713)	3,8 mL/min/1,73 m²	– 1,84; 9,51	0,1842	N/A	N/A	N/A	Analysis of Covariance (ANCOVA) model, adjusting for treatment group, baseline eGFR, race, and region, Data for patients who died were imputed as 0 (composite strategy), Other missing data were handled via multiple imputation, Intercurrent	REGENCY (79)
	Placebo	136	- 1,5 mL/min/1,73 m² (SE: 2,706)								

Results of REGENCY (NCT04221477)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95 % CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										events (rescue, treatment failure) were handled using a treatment policy strategy (using observed data regardless of the event),	
Death or renal-related events through Week 76	Obi	135	18,9% (12,11, 25,61)	– 16,8%	– 27,50, – 6,23	0,0026	N/A	N/A	N/A	CMH test stratified by region and race, Early study withdrawal due to lack of efficacy was considered an event (composite strategy), Other missing data were imputed via multiple imputation,	REGENCY (79)
	Placebo	136	35,6% (27,50, 43,78)								
ORR at Week 50	Obi	135	59,1% (50,80, 67,43)	8,4%	−3,41, 20,12	0,1670	N/A	N/A	N/A	CMH test stratified by region and race, Missing values were handled via multiple imputation (FCS predicted mean matching),	REGENCY (79)
	Placebo	136	50,7% (42,16, 59,22)								
Change in FACIT-F from	Obi	135	1,8 points (SE: 1,22)	– 1,4 points	−3,89, 1,20	0,2991	N/A	N/A	N/A	ANCOVA model adjusting for treatment, baseline value,	REGENCY (79)

Results of REGENCY (NCT04221477)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95 % CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
baseline to Week 76	Placebo	136	3,1 points (SE: 1,21)							race, and region, Data for patients who died were imputed as 0, Other intercurrent event were handled using the Treatment Policy Strategy, meaning observed data were used regardless of the event,	
Total peripheral B-cell (CD19) count at Week 76 (TBNK)	Obi	128	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Summarized descriptively (mean, median) over time by treatment group,	CSR (59)
	Placebo	125	[redacted]								
Total peripheral B-cell (CD19) count at Week 76 (HSFC)	Obi	128	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Summarized descriptively (mean, median) over time by treatment group,	CSR (59)
	Placebo	125	[redacted]								
	Obi	135	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		CSR (59)

Results of REGENCY (NCT04221477)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95 % CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Time to LN flare from Week 24 through Week 76	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]				Summary statistics of time to LN flare from Week 24 (median, percentiles) are Kaplan-Meier estimates, 95% CI for Median was computed using the methods of Brookmeyer and Crowley, Hazard ratio was estimated by Cox regression with the stratification factors race and region, Patients who experienced early study withdrawal before an event were censored at the time of withdrawal, Patients completing the 76-week period without an event were censored at the upper limit of the Week 76 visit window,	
	Placebo	136	[redacted]								

Change in SLEDAI-2K from baseline to Week 76

The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) is a validated instrument to assess SLE disease activity, It evaluates clinical symptoms and laboratory markers across nine organ systems and was used to capture changes in lupus-related disease activity, SLE manifestations are assessed by the clinician if present within the last 30 days and added to determine the total SLEDAI-2K score, which ranges from 0 to 105, Patients experiencing the intercurrent events of rescue therapy, treatment failure or study treatment discontinuation were evaluated using their observed data under the treatment policy strategy, Data after the intercurrent event death was imputed with 105 under composite strategy, Missing data was imputed by multiple imputations using fully conditional specification (FCS) predicted mean matching method, Only patients who did not die were included in the imputation model, The analysis was performed using analysis of covariance (ANCOVA) model with treatment group (combined obinutuzumab vs placebo), baseline total SLEDAI-2K score and the stratification factors race and region included as independent variables,

[redacted]

Subgroup analyses

Pre-specified subgroup analyses of the primary endpoint based on key baseline risk factors showed a generally consistent treatment benefit in favour of obinutuzumab across different subgroups, including subgroups which are indicative of high disease activity at baseline: 24-hour UPCR ≥ 3 g/g, anti-dsDNA > 120 kU/L, C3 < 0,9 g/L, C4 < 0,1 g/L and presence of concomitant Class V lupus nephritis,

All analyses are exploratory in nature and should be interpreted with caution, particularly for subgroups with a small sample size,

Figure 10 Forest plot of difference in proportion of patients in CRR at Week 76 by subgroup (Efficacy-Evaluable Population)

Appendix C. Comparative analysis of efficacy

N/A

Table 44 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		

Appendix D. Extrapolation

N/R

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

N/R

Appendix E. Serious adverse events

In this section serious adverse events from the clinical trial CA41705 REGENCY are listed, In the Table 45 investigator text for AEs has been encoded using MedDRA version 27,0, Only treatment emergent SAEs are displayed, For frequency counts by preferred term, multiple occurrences of the same SAE in an individual are counted only once, For frequency counts of "Total number of events", multiple occurrences of the same AE in an individual are counted separately,

Includes AEs through 76 weeks blinded treatment period, Includes AEs until the point of rescue for patients who received rescue therapy (except corticosteroid-only rescue), All patients received standard of care, consisting of MMF and corticosteroids, as per protocol,

Table 45 Serious adverse events, CA41705 REGENCY, safety evaluable population, CCOD 15 August 2024 (78, 79),

MedDRA System Organ Class MedDRA Preferred Term	**Obinutuzumab (N=136)**	**Placebo (N=132)**
Total number of patients with at least one adverse event	44 (32,4%)	24 (18,2%)
Overall total number of events	68	35
Infections and infestations		
Total number of patients with at least one adverse event	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]
COVID-19 pneumonia	7 (5,1%)	0
Pneumonia	4 (2,9%)	3 (2,3%)
Urinary tract infection	4 (2,9%)	2 (1,5%)
COVID-19	4 (2,9%)	1 (0,8%)
Gastroenteritis	3 (2,2%)	2 (1,5%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=136)	Placebo (N=132)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Renal and urinary disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Acute kidney injury	3 (2,2%)	2 (1,5%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders		
[redacted]	[redacted]	[redacted]

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=136)	Placebo (N=132)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Gastrointestinal disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=136)	Placebo (N=132)
Vascular disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Hepatobiliary disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders		

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=136)	Placebo (N=132)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Cardiac disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Investigations		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Nervous system disorders		

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=136)	Placebo (N=132)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Eye disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Corticosteroids exposure

Corticosteroid exposure was evaluated in the safety-evaluable population, Treatment duration is defined as the number of days on which a patient received corticosteroids, Premedication with methylprednisolone (80 mg IV) was not included, Total dose represents the prednisone equivalent dose, Only corticosteroids administered PO, IV, and IM are included, Data includes the period until the point of rescue for patients who received rescue therapy (except corticosteroid-only rescue) and covers the 76-week blinded treatment period,

Figure 11 Corticosteroids exposure, Safety-Evaluable Population

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

Transition probabilities, number of adverse events and utilities are varied in the PSA, see Table 46 below, For the transition probabilities a Dirichlet distribution is assumed, The Dirichlet distribution, which is the multinomial equivalent of the beta distribution, is suitable for scenarios with more than two possible transitions

As the Dirichlet distribution is not a part of the Excel package, we have used the method provided by Briggs 2006 (92) to sample values under the assumption of a Dirichlet distribution, This is done in column AB-AX of the CEM within the sheet "Transition Matrices", The procedure is the following:

1. **Generate Initial Gamma Draws:** For a given set of possible transitions (e,g,, three-way transition from State B to remaining in State B, or moving to State C, or moving to State D), the method involves normalizing a draw from independent single-parameter gamma distributions, The single parameter for each gamma distribution is the number of events corresponding to that transition, It's important to note that a single-parameter gamma distribution is a special case of the usual two-parameter distribution where the second (beta) parameter is set to 1, Therefore, for each transition, a random draw from a gamma distribution is generated with the alpha parameter set to the relevant event count and the beta parameter equal to 1,

2. **Address Gamma Distribution Limitations for High Alpha Values:** A common issue in computational environments is that the gamma distribution may fail to find a solution when the alpha parameter is very high (e,g,, over 300) due to iterative solving procedures, However, for high alpha values in the single-parameter gamma function, the resulting distribution approaches a normal distribution with minimal skew, The solution to this problem is to substitute a random draw from a normal distribution when alpha is high, The mean and variance of this normal distribution should be equivalent to those of the gamma distribution, Recall that for a gamma distribution, the variance is given by $\alpha * \beta 2$, Since $\beta=1$ for the single-parameter gamma, the variance simplifies to α, Therefore, for high alpha values, a random draw from a normal distribution with a mean equal to alpha and a variance equal to alpha is used, This can be implemented with a conditional statement to automatically select the appropriate distribution,

3. **Calculate Probabilities:** Once valid numerical draws are obtained for each transition (either from the gamma or substituted normal distribution), the corresponding probability for each transition is calculated, This is done by dividing each individual draw by the sum of all the draws for that set of transitions, This normalization step ensures that all calculated probabilities are within the range of 0 to 1 and that their sum equals 1, thus forming your first Dirichlet distribution,

4. **Repeat for Additional Transition Sets:** This three-step procedure can then be repeated for other sets of probabilities associated with different states or transition scenarios (e,g,, for four probabilities associated with State A),

Table 46, Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
AE number of events Obinutuzumab				
Acute kidney injury	[redacted]	[redacted]	[redacted]	Log-normal
COVID-19	[redacted]	[redacted]	[redacted]	Log-normal
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	Log-normal
Gastroenteritis	[redacted]	[redacted]	[redacted]	Log-normal
Hypertension	[redacted]	[redacted]	[redacted]	Log-normal
Infusion related reaction	[redacted]	[redacted]	[redacted]	Log-normal
Intervertebral disc disorder	[redacted]	[redacted]	[redacted]	Log-normal
Large intestinal stenosis	[redacted]	[redacted]	[redacted]	Log-normal
Neutropenia	[redacted]	[redacted]	[redacted]	Log-normal
Pneumonia	[redacted]	[redacted]	[redacted]	Log-normal
Small intestinal obstruction	[redacted]	[redacted]	[redacted]	Log-normal
Urinary tract infection	[redacted]	[redacted]	[redacted]	Log-normal
AE number of events MMF				
Acute kidney injury	[redacted]	[redacted]	[redacted]	Log-normal
Gastroenteritis	[redacted]	[redacted]	[redacted]	Log-normal
Hypertension	[redacted]	[redacted]	[redacted]	Log-normal
Nephrotic syndrome	[redacted]	[redacted]	[redacted]	Log-normal
Pneumonia	[redacted]	[redacted]	[redacted]	Log-normal
Urinary tract infection	[redacted]	[redacted]	[redacted]	Log-normal
Cholecystitis	[redacted]	[redacted]	[redacted]	Log-normal
Pain in extremity	[redacted]	[redacted]	[redacted]	Log-normal
Utilities - Obinutuzumab				

CKD_1_3b_AD	[redacted]	[redacted]	[redacted]	Beta
CKD_1_3b_PR	[redacted]	[redacted]	[redacted]	Beta
CKD_1_3b_CR	[redacted]	[redacted]	[redacted]	Beta
Utilities - MMF				
CKD_1_3b_AD	[redacted]	[redacted]	[redacted]	Beta
CKD_1_3b_PR	[redacted]	[redacted]	[redacted]	Beta
CKD_1_3b_CR	[redacted]	[redacted]	[redacted]	Beta
Utility value for all treatments				
CKD4: Complete Response	[redacted]	[redacted]	[redacted]	Beta
CKD4: Partial Response	[redacted]	[redacted]	[redacted]	Beta
CKD4: Active Disease	[redacted]	[redacted]	[redacted]	Beta
CKD5: Dialysis	[redacted]	[redacted]	[redacted]	Beta
CKD5: Transplant	[redacted]	[redacted]	[redacted]	Beta
Various				
Age	42,00	21,42	62,58	Normal
Body weight	67,28	46,70	87,86	Normal
Treatment duration	6,00	4,82	7,18	Normal
Transition probabilities Obi+mmf+pds				
Obi+mmf+pds CKD_1_3b_AD to CKD_1_3b_AD	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_1_3b_AD to CKD_1_3b_PR	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_1_3b_AD to CKD_1_3b_CR	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_1_3b_AD to CKD_4_AD	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_1_3b_PR to CKD_1_3b_AD	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_1_3b_PR to CKD_1_3b_PR	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_1_3b_PR to CKD_1_3b_CR	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_1_3b_CR to CKD_1_3b_AD	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_1_3b_CR to CKD_1_3b_PR	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_1_3b_CR to CKD_1_3b_CR	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_4_AD to CKD_4_AD	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_4_AD to CKD_5_D	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_5_D to CKD_5_D	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_5_D to CKD_5_T	[redacted]	N/A	N/A	Dirichlet

Obi+mmf+pds CKD_5_T to CKD_5_D	[redacted]	N/A	N/A	Dirichlet
Obi+mmf+pds CKD_5_T to CKD_5_T	[redacted]	N/A	N/A	Dirichlet
Transition probabilities mmf+pds				
mmf+pds CKD_1_3b_AD to CKD_1_3b_AD	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_1_3b_AD to CKD_1_3b_PR	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_1_3b_AD to CKD_1_3b_CR	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_1_3b_AD to CKD_4_AD	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_1_3b_PR to CKD_1_3b_AD	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_1_3b_PR to CKD_1_3b_PR	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_1_3b_PR to CKD_1_3b_CR	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_1_3b_CR to CKD_1_3b_AD	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_1_3b_CR to CKD_1_3b_PR	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_1_3b_CR to CKD_1_3b_CR	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_4_AD to CKD_4_AD	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_4_AD to CKD_5_D	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_5_D to CKD_5_D	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_5_D to CKD_5_T	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_5_T to CKD_5_D	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_5_T to CKD_5_T	[redacted]	N/A	N/A	Dirichlet
mmf+pds CKD_1_3b_AD to CKD_1_3b_AD	[redacted]	N/A	N/A	Dirichlet

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

This application is based on the head-to-head study, REGENCY (CA41705), which compares obinutuzumab with placebo for the treatment of patients with ISN/RPS 2003 Class III or IV lupus nephritis treated with standard-of-care therapy consisting of MMF and glucocorticoids,

According to Danish treatment guidelines for LN, MMF plus prednisone is used as standard treatment for patients with LN, The treatment used in the REGENCY trial is very much in line with the current guidelines, MMF plus prednisone is considered a relevant comparator, and a literature review has not been conducted and thus this appendix is not applicable,

Table 47 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion

Abbreviations:

Table 48 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Abbreviations:

Table 49 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search

H.1.1 Search strategies

N/A

Table 50 of search strategy table for [name of database]

No,	Query	Results
#1		

H.1.2 Systematic selection of studies

Table 51 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population			
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

Table 52 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						

H.1.3 Excluded fulltext references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

This application is based on the head-to-head study, REGENCY (CA41705), which compares obinutuzumab with placebo for the treatment of patients with ISN/RPS 2003 Class III or IV lupus nephritis treated with standard-of-care therapy consisting of MMF and glucocorticoids,

According to Danish treatment guidelines for LN, MMF plus prednisone is used as standard treatment for patients with LN, The treatment used in the REGENCY trial is very much in line with the current guidelines, MMF plus prednisone is considered a relevant comparator, and a literature review has not been conducted and thus this appendix is not applicable,

Table 53 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion

Abbreviations:

Table 54 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Table 55 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search

I.1.1 Search strategies

N/A

Table 56 Search strategy for [name of database]

No,	Query	Results
#1		88244

Literature search results included in the model/analysis:

N/A

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

J.1.1 Systematic literature review for economic input

Roche commissioned a systematic literature review (SLR) to identify and compare economic, cost, and health outcomes in lupus nephritis (LN), with a specific interest in data from adult patients with International Society of Nephrology/Renal Pathology Society (ISN/RPS) Class III/IV ±V LN, This report details the methodology and results of the economic SLR, with the intention of supporting the development of an economic model and submission of obinutuzumab in patients with Class III/IV ±V LN for health technology assessment (HTA), initially to the National Institute for Health and Care Excellence (NICE) in England and Wales, with submission to additional HTA bodies subsequently anticipated, A clinical SLR has also been conducted in conjunction with this economic review and a separate report detailing the methods and findings of the review is available, as well as a network meta-analysis (NMA) feasibility assessment,

For this economic SLR, bibliographic database searching was performed (24th June 2024) alongside searches of conference proceedings, trial registries, HTA/regulatory body websites, additional websites to identify records of interest, All searches were conducted between 30th May and 24th June 2024, 2,661 records were retrieved from the bibliographic databases following removal of duplicates, Following primary (title/abstract) screening, 685 records were included for secondary (full-text) review, of which 123 were considered relevant for inclusion against the specified inclusion/exclusion criteria (population, intervention, comparator(s), outcomes, study design/publication type [PICOS]) criteria, A further 12 records were included from supplementary searches, resulting in an evidence base including 135 records across the three economic components,

An update to the economic SLR was conducted in 2025, with bibliographic database searching performed on 3rd March 2025, alongside searches of the same conference proceedings, trial registries, HTA/regulatory body websites, and additional websites as the original SLR, 232 records were retrieved from the bibliographic databases following removal of duplicates, Following primary (title/abstract) screening, 35 records were included for secondary (full-text) review, of which 4 were considered relevant for inclusion against the specified inclusion/exclusion criteria, One further record was included from supplementary searches, resulting in 5 additional records identified in the update, and 140 records included across the three economic components for both the original and SLR update,

The included records (n=140) represented 20 economic evaluations, 93 reporting healthcare costs and/or resource use data, and 54 reporting health-related quality of life (HRQoL) data and/or health state utility values (HSUVs), The majority (n=104/140) did not report the percentage of patients that were ISN/RPS Class III/IV ±V LN (population of interest), Just over half of the included records (n=79/140) had a primary focus on LN patients, whereas a large proportion of studies related to systemic lupus erythematosus (SLE) more generally, with patients having renal involvement/LN,

Considering a further review of the included economic records in relation to the decision problem of supporting an HTA submission to NICE and development of an economic model, 16 records were identified as being of most relevance, These records consisted of one record for economic evaluations (104), two records relevant to all components (105, 106), one record for healthcare cost and/or resource use (107), and 14 records for HSUVs (108-119),

Following prioritisation of included records, only half of the HSUV studies (n=7/14) elicited utility values, and the remaining studies sourced utilities from published literature, Disutility values were reported by very few studies and when reported, were not specific to SLE/LN patients, This highlights that there is a paucity of utility data in the relevant population of ISN/RPS Class III/IV ±V LN,

Only three cost and/or resource use studies were deemed relevant, however, the population from which cost and/or resource use data was obtained was unclear in the majority of these studies (n=2/3), As a result, there is uncertainty on the generalisability of this data to the relevant population of Class III/IV ±V patients,

Only three economic evaluations (EEs) represented a UK population; of those, two of the three were recent HTA submissions from 2023 assessing voclosporin plus mycophenolate mofetil (MMF) versus a variety of comparators, Both applied a Markov model over a lifetime horizon from a UK (England and Wales/Scottland) National Health Service (NHS) perspective, with health states defined by level of chronic kidney disease (CKD), to estimate the cost effectiveness of voclosporin, The third EE considered relevant to the decision problem compared MMF with intravenous cyclophosphamide (IVC) and used a simulation (time to event) model with less than a year time horizon, It was also dated, being a 2007 publication with the analysis based on 2005 costs/inputs, All EEs were generally conducted in the population of interest; however, pure Class V patients were also included in all, It is expected that the HTAs will be the most useful source of evidence to inform data gaps in an economic model, as these are the most recent publications identified relevant to a UK population and provide a comprehensive overview of what has been submitted to UK HTA bodies to date, though any limitations of the data identified should be considered prior to inclusion in a model,

In conclusion, although a large number of records identified economic evidence, a paucity of evidence was found for the ISN/RPS Class III/IV ±V LN population, There is potential to use data from similar or proxy LN populations such as those also including pure Class V patients, or even broader LN populations, but the generalisability to the population of interest would need to be considered, HRQoL data are collected in the REGENCY study of obinutuzumab using the EQ-5D-5L, so it is expected that these data

would be the primary source of HRQoL data for inclusion within the economic model, though both sources would likely need to be mapped to the EQ-5D-3L for HTA and the suitability of using this data, alongside the generalisability to the overall population, assessed, Recent EEs conducted from a UK perspective generally support the use of a Markov model with a lifetime horizon, though there was no clear consensus on cycle length based on data reported, though the NICE voclosporin HTA applied 6-monthly cycles, It may be useful to consider other recently published EEs identified in other countries to compare similarities/differences between the model structures applied compared with the UK HTAs,

J.1.1.1 Information sources for searches

Searches for the original SLR were performed between 30th May and 24th June 2024, with updated searches performed between 24th February and 3rd March 2025, All searches were undertaken according to published SLR methods of the Cochrane Collaboration (120) and the CRD (York, UK) (121) to reduce the risk of bias and error,

Bibliographic database searches were conducted in relevant databases of published research, with a single search strategy designed to identify evidence across all three economic components (economic evaluations, healthcare costs and/or resource use, HRQoL and HSUVs),

Alongside bibliographic database searches, relevant conference proceedings were searched either via the bibliographic databases or through hand-searching, Additional hand-searching was also conducted to identify economic data reported on global/HTA regulatory body websites, additional websites/sources of information, and through reference-tracking of systematic reviews,

The following sources were searched to identify relevant publications:

- Electronic bibliographic databases
- Conference proceedings (automatically identified in the bibliographic database searches or hand-searched)
- Global HTA/regulatory bodies
- Additional websites/sources of information
- Reference lists of publications (specifically including SLRs identified from the bibliographic databases)

Table 57 Bibliographic databases

Database/information source	Interface/website URL	Date of original search	Date of update search
Embase®, 1974 to present	http://ovidsp.ovid.com/Cochrane Library/Wiley	24th June 2024	3rd March 2025
MEDLINE®, 1946 to present, including: • MEDLINE Epub Ahead of Print	http://ovidsp.ovid.com/Cochrane Library/Wiley	24th June 2024	3rd March 2025

Database/information source	Interface/website URL	Date of original search	Date of update search
• MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily			
Evidence-Based Medicine (EBM) Reviews, incorporating: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effects (DARE) (1991–2015) • HTA database (2001–2016) • National Health Service Economic Evaluation Database (NHS EED) (1995–2015)	http://ovidsp,ovid,com/Cochrane Library/Wiley	24th June 2024	3rd March 2025 – DARE, HTA database, and NHS EED were not searched for the update as the databases are no longer maintained and will not have been updated since the original review
EconLit, 1886 to present	Ovid/www,embase,com	24th June 2024	3rd March 2025

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; EBM, Evidence-Based Medicine; HTA, health technology assessment; NHS EED, National Health Service Economic Evaluation Database,

Table 58, Conference proceedings

Conference name	Interface/website	Date of original search	Date of update search

International Society for Pharmacoeconomics and Outcomes Research (ISPOR; Europe and US)	**ISPOR Europe – indexed in Embase (2021-2023);** 2024 conference scheduled for late 2024, so abstracts were unavailable during search period *2021: Value in Health, Volume 24, Issue 12, S2 (December 2021)* *2022: Value in Health, Volume 25, Issue 12S (December 2022)* *2023: Value in Health, Volume 26, Issue 11, S2 (December 2023)* **ISPOR US – pre-2024 indexed in Embase (2021–2023), 2024 ISPOR US conference hand-searched** *2021: Value in Health, Volume 24, Issue 5, S1 (May 2021)* *2022: Value in Health, Volume 25, Issue 6, S1 (June 2022)* *2023: Value in Health, Volume 26, Issue 6, S2 (June 2023)* *2024: Value in Health, Volume 27, Issue 6, S1 (June 2024)*	30th May 2024 (hand-searching); 24th June 2024 (Embase)	Europe: 3rd March 2025 (Embase) US: 2024 event captured in original searches
Health Technology Assessment International (HTAi)	https://htai,org/annual-meetings/ **2022 and 2023 conferences hand-searched** **2021 conference proceedings abstract book unavailable (online link did not work)** **2024 conference scheduled for June 2024 and abstracts were unavailable during search period**	30th May 2024	3rd March 2025 (Embase)
International Health Economics Association (IHEA)	https://healtheconomics,org/congress/ (biennial conference) **2021 and 2023 conferences hand-searched**	30th May 2024	No 2024 event to search
American College of Rheumatology (ACR) Convergence	https://acrabstracts,org/meetings-archive/ **Pre-2023 indexed in Embase** **2023 conference hand-searched** https://acrabstracts,org/meetings/acr-convergence-2023/ 2024 conference scheduled for late 2024, so abstracts were unavailable during search period	30th May 2024 (hand-searching); 24th June 2024 (Embase)	26th February 2025
American Society of Nephrology (ASN)	Kidney Week Journal of the American Society of Nephrology, Kidney Week Abstract Supplement https://www,asn-online,org/education/kidneyweek/archives/ **Indexed in Embase**	24th June 2024	3rd March 2025 (Embase)

European Renal Association (ERA)	https://www,era-online,org/events/ Nephrology Dialysis Transplantation **2021–2024 conferences hand-searched** 2021: Nephrology Dialysis Transplantation, Volume 36, Issue Supplement_1, May 2021; https://academic,oup,com/ndt/issue/36/Supplement_1 2022: Nephrology Dialysis Transplantation, Volume 37, Issue Supplement_3, May 2022; https://academic,oup,com/ndt/issue/37/Supplement_3 2023: Nephrology Dialysis Transplantation, Volume 38, Issue Supplement_1, June 2023; https://academic,oup,com/ndt/issue/38/Supplement_1 2024: Nephrology Dialysis Transplantation, Volume 39, Issue Supplement_1, May 2024; https://academic,oup,com/ndt/issue/39/Supplement_1	30th May 2024	2024 event captured in original searches
European Alliance of Associations for Rheumatology (EULAR)	https://congress,eular,org/about,cfm Annals of the Rheumatic Diseases **2022–2023 conferences hand-searched** **2021 conference proceedings abstract book unavailable (table of contents only)** **2024 conference scheduled for June 2024 and abstracts were unavailable during search period** 2021: Annals of the Rheumatic Diseases, Vol, 80, Issue Suppl 1; https://ard,bmj,com/content/80/Suppl_1 2022: Annals of the Rheumatic Diseases, Vol, 81, Issue Suppl 1; https://ard,bmj,com/content/81/Suppl_1 2023: Annals of the Rheumatic Diseases, Vol, 82, Issue Suppl 1; https://ard,bmj,com/content/82/Suppl_1	30th May 2024	3rd March 2025 (Embase)
International Congress on Systemic Lupus Erythematosus (ICSLE)	(biennial conference) **2021 and 2023 conferences hand-searched** 2021: https://lupus2021,kenes,com 2023: https://www,lupus-kcr2023,org/; Lupus Science & Medicine, Volume 10, Suppl 1; https://lupus,bmj,com/content/10/Suppl_1	30th May 2024	No 2024 event to search

Pan American League of Associations for Rheumatology (PANLAR)	https://congreso-panlar,com/en Journal of Clinical Rheumatology **2021–2024 conferences hand-searched** 2021: Journal of Clinical Rheumatology, Volume 27 Issue 5S 2022: Journal of Clinical Rheumatology, Volume 28 Supplement 1 2023: Journal of Clinical Rheumatology, 29(4 Supplement 1) 2024: https://globalrheumpanlar,org/articulo/abstracts-panlar-2024-2008	30th May 2024	2024 event captured in original searches
European Lupus Society (SLEuro)	https://sleuro,org/past-meetings/ (biennial conference) Lupus Science & Medicine Journal **2022 and 2024 conferences hand-searched** 2022: Lupus Science & Medicine, Vol 9, Suppl 2; https://lupus,bmj,com/content/9/Suppl_2 2024: Lupus Science & Medicine, Vol 11, Suppl 1; https://lupus,bmj,com/content/11/Suppl_2	30th May 2024	2024 event captured in original searches
Annual meeting of Lupus Academy	https://lupus-academy,org/library/abstract-books Lupus Science & Medicine Journal **Indexed in Embase**	24th June 2024	3rd March 2025 (Embase)
World Congress of Nephrology (WCN)	https://www,theisn,org/wcn/ https://www,kireports,org/issues **Indexed in CENTRAL database**	24th June 2024	3rd March 2025 (CENTRAL)

Table 59, Global HTA Bodies searched

National Institute for Health and Care Excellence (NICE) [England & Wales]	Interface/website	Date of original search	Date of update search
Scottish Medicines Consortium (SMC) [Scotland]	https://www,nice,org,uk/	17th June 2024	24th February 2025
Canadian Agency for Drugs and Technologies in Health (CADTH) (now Canada's Drug Agency [CDA-AMC]),	https://www,scottishmedicines,org,uk	17th June 2024	24th February 2025

including the pan-Canadian Oncology Drug Review (pCODR) [Canada]			
Institut national d'excellence en santé et en services sociaux (INESSS) [Canada]	https://www,cadth,ca/ (website now https://www,cda-amc,ca)	17th June 2024	24th February 2025
Pharmaceutical Benefits Advisory Committee (PBAC) [Australia]	https://www,inesss,qc,ca/en/home,html	17th June 2024	24th February 2025
Haute Autorité de Santé (HAS) [France]	https://www,pbs,gov,au/pbs/home	17th June 2024	24th February 2025
Institute for Quality and Efficiency in Health Care (IQWiG) [Germany]	https://www,has-sante,fr/	17th June 2024	24th February 2025
Institute for Clinical and Economic Review [US]	https://www,iqwig,de/	17th June 2024	24th February 2025
European Medicines Agency (EMA) [EU regulatory]	https://icer-review,org/	17th June 2024	24th February 2025
U,S, Food and Drug Administration (FDA) [US]	https://www,ema,europa,eu/en	17th June 2024	24th February 2025
	https://www,fda,gov/	17th June 2024	24th February 2025

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CDA-AMC, Canada's Drug Agency; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; HAS, Haute Autorité de Santé; HTA, health technology assessment; INESSS, Institut national d'excellence en santé et en services sociaux; IQWiG, Institute for Quality and Efficiency in Health Care; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; pCODR, pan-Canadian Oncology Drug Review; SMC, Scottish Medicines Consortium,

Table 60, Additional sources

Source name	Interface/website	Date of original search	Date of update search

EuroQoL website	https://euroqol,org/	30th May 2024	26th February 2025
CEA registry	https://cear,tuftsmedicalcenter,org/	30th May 2024	26th February 2025
RePEc website (EconPapers)	https://econpapers,repec,org/	30th May 2024	26th February 2025
International Network of Agencies for Health Technology Assessment (INAHTA) International HTA database	https://database,inahta,org/	30th May 2024	26th February 2025
National Institute for Health Research (NIHR)	https://www,nihr,ac,uk/	30th May 2024	26th February 2025

Abbreviations: CEA, cost-effectiveness analysis; HTA, health technology assessment; INAHTA, International Network of Agencies for Health Technology Assessment; NIHR, National Institute for Health and Care Research; RePEc, Research Papers in Economics,

J.1.1.2 Prisma Diagram

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; HSUV, health state utility value; HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review,
† Included articles may be relevant to more than one economic component (cost effectiveness, healthcare cost and/or resource use, HSUV),
‡ Duplicates included publications that were identified in the original review that were not deduplicated in KiaKia due to the update being run as a separate review,

J.1.2 Targeted literature search for transition probabilities across CKD stages to inform an Economic Model

Objectives

The objective of this targeted literature review (TLR) was to identify and summarize evidence on probabilities of chronic kidney disease (CKD) stage transitions, response rates to treatment, and mortality risks by CKD stage, specifically to inform an economic model evaluating the cost-effectiveness of obinutuzumab in lupus nephritis (LN),

A targeted search strategy using artificial intelligence-enabled searches and expert human oversight was conducted, Relevant studies published since 2015 were identified from key regions including the United States (US), Canada, the United Kingdom (UK), Germany, Italy, France, Spain, and Australia, The review included two main types of evidence sources: economic evaluations (published and HTA-submitted cost-

effectiveness analyses) and real-world observational cohort studies, Extracted outcomes encompassed CKD progression probabilities, renal response rates (complete and partial), and mortality probabilities from various CKD stages,

Methods

A targeted search strategy using artificial intelligence-enabled searches and expert human oversight was conducted, Relevant studies published since 2015 were identified from key regions including the United States (US), Canada, the United Kingdom (UK), Germany, Italy, France, Spain, and Australia, The review included two main types of evidence sources: economic evaluations (published and HTA-submitted cost-effectiveness analyses) and real-world observational cohort studies, Extracted outcomes encompassed CKD progression probabilities, renal response rates (complete and partial), and mortality probabilities from various CKD stages,

Results

Eleven economic evaluations (85, 86, 122-130) were identified, including eight LN-specific analyses (4 HTAs (85, 124, 126, 127) and 4 publications (86, 122, 123, 125)) and three broader CKD-focused studies (1 HTA (130), 1 SLR (86), 1 risk-prediction model (129)), Most economic models adopted a Markov cohort (85, 122, 124-128, 130) or hybrid Markov-partitioned-survival structure (85, 124, 128) and compared interventions such as voclosporin (122, 125, 126, 128), belimumab (85, 124, 127), dapagliflozin (130), and mycophenolate mofetil (MMF) (122),

Only the economic evaluations analysing LN patients reported inputs for partial and complete renal response (CRR), given the response-based health states used in these studies (85, 124-126, 128), The response data were derived from the pivotal trials of the LN treatments but were not stratified by CKD stages, The NICE submission of voclosporin (125) used a zero probability of complete and partial response for the cohort in CKD stage 3b-4, citing a lack of data, Short-term complete renal response rates at one year were comparable across trials, while heterogeneity was observed in 1-year partial response rates,

The evidence available from the economic evaluations to inform the transition probability from CKD stages 1-3b to CKD stage 4 and from CKD stage 4 to CKD stage 5 was scattered, Early-stage transitions are mainly available from the general-CKD population (86, 130) while LN-specific data are available only from the voclosporin NICE HTA (125) (sourced from expert elicitation, citing lack of published data to inform these transitions),

In terms of all-cause mortality, two LN models (85, 124) rely on observed deaths in their respective trial populations; a third LN study (122) overlays trial survival with registry-based dialysis hazards; and three CKD-focused sources (86, 129, 130) contribute stage-specific death rates for the general CKD population, Significant variability was noted, highlighting uncertainty and the need for careful calibration in economic modelling, One study (122) applied an explicit LN-specific multiplier (age-adjusted hazard ratio), underscoring the paucity of disease-specific survival data outside stage 5, Lupus-related death by remission and relapse status was reported by only one study (122),

Eleven observational cohort studies were reviewed population (44, 131-140), of which four examined the LN population (131-134) while the remaining seven examined the CKD population (44, 135-140), These studies were primarily retrospective analyses leveraging registry or administrative data,

Only one real-world study reported kidney function trajectories in LN (132), and three in the broader CKD population (44, 136, 138), LN data were informed by the US Medicaid cohort that recorded an all-stage ESRD incidence of 14,3% over 3,1 years (132), Collectively, the studies consistently demonstrated a consistent rise in progression risk with advancing baseline CKD stage, but absolute risks—particularly for early-stage transitions to ESRD—varied two- to ten-fold, indicating moderate cross-study heterogeneity,

None of the studies reported data on partial or CS in patients with LN or CKD,

Eight out of 11 real-world cohort studies (four in LN (131-134) and four in the CKD population (44, 135, 136, 140)) reported mortality outcomes drawn almost exclusively from national or regional renal registries, Directionally, the evidence consistently showed high mortality associated with dialysis, whereas kidney transplantation significantly improved survival, However, absolute risks varied two- to threefold, indicating moderate heterogeneity across studies,

Implications for Economic model

This targeted review identified critical evidence gaps for the economic modelling of obinutuzumab in LN, In particular, LN-specific progression data from early CKD stages to stage 4 remain scarce, necessitating reliance on general CKD data, The durability of long-term renal responses beyond the initial few years also remains uncertain due to the limited follow-up duration in available trials, Additionally, the transition from CKD stage 4 to dialysis carries significant model leverage, warranting further validation through structured expert elicitation or additional real-world analyses, Given the heterogeneity observed in transition and mortality probabilities, the economic model for obinutuzumab should incorporate robust sensitivity analyses and probabilistic approaches to adequately address and quantify parameter uncertainty,

Appendix K. MSM model used to estimate transitions from CKD1-3b CR and PR

This section describes how transitions are calculated from CKD 1-3b CR and PR towards other health states where a multi state Markov model is used,

This analysis uses data from the REGENCY study, where individuals with lupus nephritis were assessed at **Week 24**, **Week 50**, and **Week 76**, We used the msm package in R (version 4,4,3) to model transitions between four distinct health states:

- **Active Disease (AD)**
- **Complete Renal Response (CRR)**
- **Partial Renal Response (PRR)**, exclusive of CRR
- **Death** (an absorbing state)

All individuals began in the Active Disease state at baseline, The exact date of death was known for the few patients who died,

The analysis included [redacted] (pooled analysis with patients from both treatment arms), The number of post-baseline observations per patient was:

[redacted]

Following the REGENCY study's protocol for handling intercurrent events, individuals who died or discontinued the study were classified as non-responders[redacted]

The tables below show the observed frequencies of transitions between states for all patients, i,e, both treatments arms, The states are numbered as follows: 1=AD, 2=CRR, 3=PRR, 4=Death,

Table 61, Overall Transition Counts

From	To: AD (1)	To: CRR (2)	To: PRR (3)	To: Death (4)
AD (1)	[redacted]	[redacted]	[redacted]	[redacted]

CRR (2)	[redacted]	[redacted]	[redacted]	[redacted]
PRR (3)	[redacted]	[redacted]	[redacted]	[redacted]

Using the msm package, the 6-month transition probability matrices were estimated, The values represent the probability of moving from a state in a given row to a state in a given column over a 6-month period,

Table 62, Overall 6-Month Transition Probabilities

From	To: AD (1)	To: CRR (2)	To: PRR (3)	To: Death (4)
AD (1)	[redacted]	[redacted]	[redacted]	[redacted]
CRR (2)	[redacted]	[redacted]	[redacted]	[redacted]
PRR (3)	[redacted]	[redacted]	[redacted]	[redacted]
Death (4)	[redacted]	[redacted]	[redacted]	[redacted]

Appendix L. HSUVs Model selection

[redacted]

[redacted]

Appendix M. Health state frequencies

Table 63 provides an overview of the frequencies of resource usage for the model's respective health states, These can also be identified from the Excel model within the sheet "Supportive Care Costs",

Table 63, Disease management frequencies

	CKD_1_3b_CR		CKD_1_3b_PR		CKD_1_3b_AD		CKD_4_CR		CKD_4_PR		CKD_4_AD		CKD_5_D		CKD_5_T	
	One off cost	Recurrent Costs	One off cost	Recurrent Costs	One off cost	Recurrent Costs	One off cost	Recurrent Costs	One off cost	Recurrent Costs	One off cost	Recurrent Costs	One off cost	Recurrent Costs	Cost of first plus second cycle	Cost of third and following cycles
Nurse visit	1	1	4	2	6	3	2	2	4	3	6	3				
Specialist visit	1	1	4	2	6	3	2	2	4	3	6	3	6	3		
Psychologist													6	2		
Kidney biopsy											1					
Urinalysis (includes eGFR, serum albumin, proteinuria and urinary sediment)	2	2	7	4	12	6	4	4	8	5	12	6				
Complete blood count	2	2	7	4	12	6	4	4	8	5	12	6				

Serum immunoglobulin measurement	1	1	6	3	1 2	6	1	1	6	3	1 2	6								
Antibody tests	1	1	6	3	1 2	6	1	1	6	3	1 2	6								
Chronic infection screening	1	1	6	3	1 2	6	1	1	6	3	1 2	6								
Cholesterol and lipid monitoring	1	1	6	3	1 2	6	1	1	6	3	1 2	6								
Anti-dsDNA and C3 and C4 level monitoring	2	2	7	4	1 2	6	4	4	8	5	1 2	6								
Dialysis													1	1						
Initial assessment for kidney transplant													1							
Waiting list clinic attendance (pre-transplant)													2	2						
Kidney transplantation															1					
Post-kidney transplantation, year 1															1					
Post-kidney transplantation, year 2+																1				

Vitamin D supplements							1	1	1	1	1	1	1	1	1	1
ESAs and EPO							1	1	1	1	1	1	1	1	1	1
Phosphate binders							1	1	1	1	1	1	1	1	1	1
ACEI or ARB	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Anti-hypertensive medication	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ultrasound											1					
Echocardiogram	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

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