16 October 2025
EMADOC-1700519818-2313995
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gazyvaro

International non-proprietary name: Obinutuzumab

Procedure No. EMA/VR/0000244907

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADR	adverse drug reactions
AE	adverse event
AESI	adverse event of special interest
anti-dsDNA	anti-double-stranded DNA
AUC	area under the concentration-time curve
AZA	azathioprine
BCFU	B cell follow-up
BLyS	B-lymphocyte stimulator
CCOD	clinical cut-off date
CDC	complement-dependent cytotoxicity
CLL	chronic lymphocytic leukemia
CMH	Cochrane Mantel Haenszel
CNI	calcineurin inhibitor
CRR	complete renal response
CSR	clinical study report
CYC	cyclophosphamide
DCD	direct cell death
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESKD	end-stage kidney disease
FACIT-F	Functional Assessment of Chronic Illness Therapy Fatigue
FDA	U.S. Food and Drug Administration
FL	follicular lymphoma
GCP	Good Clinical Practice
ISN	International Society of Nephrology
IRR	infusion-related reaction
KDIGO	Kidney Disease: Improving Global Outcomes
LLN	lower limit of normal
MAA	Marketing Authorisation Application
mAb	monoclonal antibody

mITT	modified intent to treat
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MPAA	mycophenolic acid analogs
NK	natural killer
Obi	obinutuzumab
OLT	open label treatment
ORR	overall renal response
Pcb	placebo
PD	pharmacodynamic
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PopPK	population pharmacokinetics
PRO	patient reported outcome
PRR	partial renal response
PT	preferred term
RAAS	renin angiotensin-aldosterone system
RPS	Renal Pathology Society
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SLE	Systemic Lupus Erythematosus
SOC	System Organ Class
UPCR	urinary protein-to-creatinine ratio
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 7 January 2025 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB

Extension of indication to include treatment of adult patients with active lupus nephritis who are receiving standard therapy for GAZYVARO, based on results from study Regency (CA41705). This is an ongoing, Phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of obinutuzumab administered at standard infusion rates in patients with ISN/RPS 2003 Class III or IV lupus nephritis treated with standard-of-care therapy.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

Information relating to orphan designation

Gazyvaro, was designated as an orphan medicinal product EU/3/15/1504 on 19 June 2015 in the following indication: treatment of follicular lymphoma.

The new indication, which is the subject of this application, does not fall within any orphan designation. According to Article 7 of Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, it is not possible to combine an orphan indication and a non-orphan indication in the same marketing authorisation. Consequently, the MAH has committed to request the withdrawal of the orphan designation from the Community Register of Orphan Medicinal Products within 2 days after the receipt of the CHMP opinion. On 15th of October 2025, the MAH has submitted the withdrawal request for the orphan designation EU/3/15/1504.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0296/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0296/2022 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received scientific advices from the CHMP (EMEA/H/SA/3467/2/2019/III and EMEA/H/SA/3467/2/FU/1/2020/II). The advices pertained to the non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Boje Kvorning Pires Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	07 January 2025
Start of procedure:	26 January 2025
CHMP Rapp AR	18 March 2025
PRAC Rapporteur Assessment Report	28 March 2025
PRAC members comments	02 April 2025
Updated PRAC Rapp AR	03 April 2025
PRAC Outcome	09 April 2025
CHMP members comments	14 April 2025
Updated CHMP Rapp AR	15 April 2025
1st CHMP RSI	25 April 2025
Submission of responses	22 May 2025
Restart date	26 May 2025
CHMP Rapp AR	23 June 2025
PRAC Rapp AR	27 June 2025
PRAC members comments	02 July 2025
Updated PRAC Rapp AR	03 July 2025
PRAC Outcome	10 July 2025
CHMP members comments	14 July 2025
Updated CHMP Rapp AR	18 July 2025
2nd CHMP RSI	24 July 2025
Submission of responses	12 August 2025
Restart date	18 August 2025
CHMP Rapp AR	15 September 2025
PRAC Rapp AR	19 September 2025
PRAC members comments	24 September 2025

Timetable	Actual dates
Updated PRAC Rapp AR	25 September 2025
PRAC Outcome	02 October 2025
CHMP members comments	06 October 2025
Updated CHMP Rapp AR	09 October 2025
CHMP Opinion	16 October 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease that occurs primarily in women of childbearing age. It is characterised by multisystem involvement and immunological abnormalities, and much of the tissue damage is thought to occur through autoantibody formation and immune complex deposition, which leads to tissue inflammation and destruction. Autoreactive B cells appear to play a key role in this process. Lupus nephritis is the most common organ-threatening manifestation of SLE and remains a major cause of morbidity and mortality among patients with SLE (Maria and Davidson 2020[1]; Mok et al. 2023[2]; Siegel and Sammaritano 2024[3]; Anders et al. 2020[4]). Proteinuria is the most common clinical feature of lupus nephritis and may be accompanied by haematuria, hypertension, volume overload, metabolic abnormalities, and progressive impairment of renal function.

The presence of kidney biopsy-proven proliferative nephritis, defined as ISN/RPS 2003 Class III or IV lupus nephritis, is associated with a high risk of progression to end-stage kidney disease (ESKD), even with treatment (Hanly et al. 2016[31]; Contreras et al. 2004[5]; Anders et al. 2020[4]). Progression to ESKD occurs in approximately 10% of patients within 10 years of lupus nephritis diagnosis (Tektonidou et al. 2016[6]; Siegel and Sammaritano 2024[3]; Anders et al. 2020[4]).

Claimed therapeutic indication:

Gazyvaro is indicated for the treatment of adult patients with active lupus nephritis (LN) who are receiving standard therapy.

[1] Maria NI, Davidson A. Protecting the kidney in systemic lupus erythematosus: from diagnosis to therapy. Nature reviews Rheumatology. 2020;16(5):255-67.
[2] Mok CC, Teng YKO, Saxena R, et al. Treatment of lupus nephritis: consensus, evidence and perspectives. Nat Rev Rheumatol. 2023 Apr;19(4):227-238.
[3] Siegel CH, Sammaritano LR. Systemic Lupus Erythematosus: A Review. JAMA. 2024;331(17):1480-91.
[4] Anders HJ, Saxena R, Zhao MH, et al. Lupus nephritis [review]. Nat Rev Dis Primers 2020; 6: 7.
[5] Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004;350:971-80.
[6] Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971–2015: a systematic review and Bayesian meta-analysis [review]. Arthritis Rheumatol 2016; 68: 1432–1441.

Epidemiology

The incidence of lupus nephritis varies in different estimates based on numerous population-based epidemiological studies that have been conducted globally with an overall annual incidence ranging from approximately 0.45 to 6.85 per 100,000 population per year for both sexes (Hocaoglu et al. 2023[7]; Feldman et al. 2013[8]; Hiraki et al. 2012[9]; Delarche et al. 2018; Nossent et al. 2024[10]; Patel et al. 2006[11]; Eilertsen et al. 2011[12]; Hermansen et al. 2016[13]). In Europe, population-based studies from Norway, Denmark, and the United Kingdom reported an annual incidence ranging from 0.4 to 0.6 per 100,000 population per year (Eilertsen et al. 2011[12]; Hermansen et al. 2016[13]; Patel et al. 2006[11]).

The overall prevalence of lupus nephritis ranged between 4.4 to 30.92 per 100,000 population across the globe for both sexes (Hocaoglu et al. 2023[7]; Feldman et al. 2013[8]; Hiraki et al. 2012[9]; Nossent et al. 2024[10]; Patel et al. 2006[11]; Eilertsen et al. 2011[12]; Hermansen et al. 2016[13]). In Europe, the prevalence of lupus nephritis ranged between 4.4 to 13.8 per 100,000 individuals (Hocaoglu et al. 2023[7]; Feldman et al. 2013[8]; Hiraki et al. 2012[9]; Nossent et al. 2024[10]; Patel et al. 2006[11]; Eilertsen et al. 2011[12]; Hermansen et al. 2016[13]).

In a study evaluating a cohort of 178 Norwegian, mostly Caucasian, patients with lupus nephritis from 1988 until 2007, the standardised mortality ratio for all-cause mortality among persons with lupus nephritis was 5.6 (95% CI: 3.7, 7.5), and age and Class IV lupus nephritis was associated with increased all-cause mortality (Norby et al. 2017[14]).

Management

The primary goal of treatment is to stop the active disease process in order to provide long-term preservation of kidney function and prevention of the progression of chronic kidney disease and eventual ESKD. An additional objective is to minimise glucocorticoid use as well as toxicities associated with established therapeutic interventions (Anders et al. 2020[4]; Mohan et al. 2023[15]; Kidney Disease: Improving Global Outcomes [KDIGO] 2024[16]; Hahn et al. 2012[17]).

For several decades, the standard of care therapy for patients with proliferative lupus nephritis was limited to corticosteroids in combination with either mycophenolate mofetil (MMF) or cyclophosphamide (CYC), along with antimalarials and blood pressure control with renin-angiotensin-aldosterone system

[7] Hocaoğlu M, Valenzuela-Almada MO, Dabit JY, Osei-Onomah SA, Chevet B, Giblon RE, Zand L, Fervenza FC, Helmick CG, Crowson CS, Duarte-García A. Incidence, Prevalence, and Mortality of Lupus Nephritis: A Population-Based Study Over Four Decades Using the Lupus Midwest Network. Arthritis Rheumatol. 2023 Apr;75(4):567-573.
[8] Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcón GS, Winkelmayer WC, Costenbader KH. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. Arthritis Rheum. 2013 Mar;65(3):753-63.
[9] Hiraki LT, Feldman CH, Liu J, Alarcón GS, Fischer MA, Winkelmayer WC, Costenbader KH. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. Arthritis Rheum. 2012 Aug;64(8):2669-76.
[10] Nossent JC, Keen HI, Preen DB, Inderjeeth CA. Population-wide long-term study of incidence, renal failure, and mortality rates for lupus nephritis. Int J Rheum Dis. 2024 Feb;27(2):e15079.
[11] Patel M, Clarke AM, Bruce IN, Symmons DP. The prevalence and incidence of biopsy-proven lupus nephritis in the UK: Evidence of an ethnic gradient. Arthritis Rheum. 2006 Sep;54(9):2963-9.
[12] Eilertsen GØ, Fismen S, Hanssen TA, Nossent JC. Decreased incidence of lupus nephritis in northern Norway is linked to increased use of antihypertensive and anticoagulant therapy. Nephrol Dial Transplant. 2011 Feb;26(2):620-7.
[13] Hermansen ML, Lindhardsen J, Torp-Pedersen C, Faurschou M, Jacobsen S. Incidence of Systemic Lupus Erythematosus and Lupus Nephritis in Denmark: A Nationwide Cohort Study. J Rheumatol. 2016 Jul;43(7):1335-9.
[14] Norby GE, Mjøen G, Bjørneklett R, Vikse BE, Holdaas H, Svarstad E, et al. Outcome in biopsy-proven Lupus nephritis: Evaluation of biopsies from the Norwegian Kidney Biopsy Registry. Lupus. 2017 Jul;26(8):881-885.
[15] Mohan C, Zhang T, Putterman C. Pathogenic cellular and molecular mediators in lupus nephritis. Nat Rev Nephrol. 2023;19(8):491-508.
[16] Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the management of LUPUS NEPHRITIS. Kidney Int. 2024 Jan;105(1S):S1-S69.
[17] Hahn B, McMahon MA, Wilkinson A, et al. American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis. Arthritis Care and Research 2012;64:797−808.

(RAAS) inhibitors (Fanouriakis et al. 2019[18], Hahn et al. 2012[17], Bertsias et al. 2012[19]). MMF, CYC and azathioprine (AZA) are standard of care therapies for patients with lupus nephritis in Europe but not authorised for this indication; however, they are recommended by the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis.

Recently, a B-lymphocyte stimulator (BLyS)-specific inhibitor, and a second-generation calcineurin inhibitor (CNI) immunosuppressant, were approved for for active lupus nephritis indications. Both belimumab and CNIs are recommended treatments for active lupus nephritis by the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis. Despite use of these new therapies, only a minority of patients achieve a CRR within the first 1–2 years, and the rate of progression to ESKD has not decreased in recent decades (Kale et al. 2023[20]; Mok et al. 2023[2]; Anders et al. 2020[4]).

Given the seriousness of active lupus nephritis, the limited efficacy of the current standard of care, including the recently approved therapies (belimumab and voclosporin) along with their toxicities and/or treatment-related side effects, there remains a high need for new safe and effective therapies for the treatment of active lupus nephritis.

2.1.2. About the product

Obinutuzumab is a glycoengineered, recombinant, humanised type II anti-CD20 mAb of the IgG1 isotype that specifically targets the extracellular loop of the CD20 transmembrane antigen that is expressed on the surface of non-malignant and malignant pre-B and mature B lymphocytes but not on hematopoietic stem cells, pro-B cells, and plasma cells (Mössner et al. 2010[21]; Niederfellner et al. 2011[22]; Klein et al. 2013[23]).

The B cell depleting activity of obinutuzumab relies mostly on its capacity to induce direct B cell killing and on its enhanced antibody-dependent cellular cytotoxicity (ADCC) (Mössner et al. 2010[21]; Herter et al. 2013[24]).

Glycoengineering of the Fc portion of obinutuzumab, with reduced fucose content, promotes binding affinity for FcγRIII receptors on immune effector cells, such as natural killer (NK) cells and macrophages/monocytes, resulting in greater levels of ADCC and antibody-dependent cellular phagocytosis (ADCP) (Mössner et al. 2010[21]; Herter et al. 2013[24]; Reddy et al. 2017[25]).

The binding mode of obinutuzumab and its wide elbow hinge largely induce direct cell death (DCD) while reducing complement-dependent cytotoxicity (CDC) (Mössner et al. 2010[21]; Alduaij et al. 2011[26]; Honeychurch et al. 2012[27]). Additionally, FcγRIIb activation is blunted, leading to minimized CD20 internalization and reduced levels of CDC (Mössner et al. 2010[21]; Herter et al. 2013[24]; Reddy et al.

[18] Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78:736 45.
[19] Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771 82.
[20] Kale A, Lech M, Anders HJ, et al. Lupus Nephritis: New and Emerging Biologic and Targeted Therapies. BioDrugs. 2023 Jul;37(4):463-475.
[21] Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 2010;115:4393–402.
[22] Niederfellner G, Lammens A, Mundigl O, et al. Epitope characterization and crystal structure of GA101 provide insights into the molecular basis for type I/II distinction of CD20 antibodies. Blood 2011;118:358□67.
[23] Klein C, Lammens A, Schäfer W, et al. Response to: monoclonal antibodies targeting CD20. MAbs 2013;5:337 8.
[24] Herter S, Herting F, Mundigl O, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. Mol Cancer Ther. 2013 Oct;12(10):2031-42.
[25] Reddy V, Klein C, Isenberg DA, et al. Obinutuzumab induces superior B-cell cytotoxicity to rituximab in rheumatoid arthritis and systemic lupus erythematosus patient samples. Rheumatology (Oxford) 2017;56:1227 37.
[26] Alduaij W, Ivanov A, Honeychurch J, et al. Novel type II anti-CD20 monoclonal antibody (GA101) evokes homotypic adhesion and actin-dependent, lysosome-mediated cell death in B-cell malignancies. Blood. 2011 Apr 28;117(17):4519-29.
[27] Honeychurch J, Alduaij W, Azizyan M, et al. Antibody-induced nonapoptotic cell death in human lymphoma and leukemia cells is mediated through a novel reactive oxygen species-dependent pathway. Blood. 2012 Apr 12;119(15):3523-33.

2017[25]). Obinutuzumab depletes peripheral and tissue B cells, as evidenced by data in non-human primates (Mössner et al. 2010[21]) and lupus-prone mouse models (Marinov et al. 2021[28]). In addition, obinutuzumab demonstrated greater in vitro B cell cytotoxicity and activation of NK cells than rituximab in blood samples of patients with rheumatoid arthritis and SLE (Reddy et al. 2017[25]). In the Phase II NOBILITY study, obinutuzumab administered at a dose of 1000 mg resulted in rapid and complete peripheral B cell depletion in patients with lupus nephritis, and to a greater extent than that observed with 1000 mg rituximab in the Phase III Study U2970g (hereafter referred to as LUNAR), which evaluated the efficacy and safety of rituximab in patients with lupus nephritis (Rovin et al. 2012; Furie et al. 2022**Error! Bookmark not defined.**). Overall, obinutuzumab has an enhanced ability to deplete CD20-positive B cells in comparison to type I anti-CD20 antibodies such as rituximab, a recommended therapy in the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis and may have the potential to significantly change the treatment of patients with active lupus nephritis.

Obinutuzumab is currently approved for the following indications:

- 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 (see section 5.1).
- 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.

2.2. Non-clinical aspects

Gazyvaro (obinutuzumab) has previously been approved for use in oncology indications in the European Union. The non-clinical data submitted in support of these indications in accordance with ICH guidelines S6(R1) and S9 consisted of assessment of primary pharmacodynamics, repeat-dose toxicity including assessment of fertility and pharmacokinetics/toxicokinetics, enhanced pre- and postnatal development study in cynomolgus monkeys, local tolerance, tissue cross-reactivity, *in vitro* cytokine release and haemolytic potential. The purpose of this variation was initially to seek approval for the following additional indication: *Treatment of adult patients with active lupus nephritis who are receiving standard therapy*. In Scientific Advice (EMA/CHMP/SAWP/600218/2019) given by the CHMP it was stated that the data package was still adequate for a marketing authorisation application for obinutuzumab in non-oncology indications, however it was expected to include a more elaborated assessment of carcinogenic potential in accordance with ICH guidelines S6(R1) and S1B(R1).

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. However, the MAH has provided a weight of evidence evaluation for the assessment of the carcinogenic potential of obinutuzumab, as summarized hereafter.

2.2.1. Toxicology

Carcinogenicity

In accordance with the ICH S6(R1) guidance, GLP toxicology studies with obinutuzumab have been conducted in cynomolgus monkeys with dosing up to 6 months.

[28] Marinov AD, Wang H, Bastacky SI, et al. The Type II Anti-CD20 Antibody obinutuzumab (GA101) is more effective than rituximab at depleting B cells and treating disease in a murine lupus model. Arthritis Rhsumatol 2021;73:826 36.

Conventional carcinogenicity studies using rodents are considered for any drug product including antibodies like obinutuzumab (ICH S1A). However, the feasibility to conduct such studies for obinutuzumab is limited. Obinutuzumab does not recognize the equivalent rodent CD20 molecule due to insufficient sequence homology. As per ICH S6(R1), rodent bioassays (or short-term carcinogenicity studies) with homologous products ("surrogates") are generally of limited value to assess carcinogenic potential of the clinical candidate.

Toxicology studies with obinutuzumab in cynomolgus monkeys did not identify any carcinogenicity risk.

The available results from clinical studies completed with obinutuzumab and from marketed CD20-targeting antibodies, do not suggest an increased risk compared to epidemiological data for the respective patient population.

While B cells are known to play a significant role in tumour surveillance, given the complex and often conflicting roles by which B-cell subpopulations can influence tumour progression, no firm conclusion on malignancy risk can be made based on the mechanism of action of anti-CD20 therapies. Based on the totality of data, the malignancy risk for obinutuzumab (and other anti-CD20 therapies) remains potential, and will need to be further characterised in the post-marketing environment. Long term safety in LN patients was included in the RMP as missing information. The long-term part of the REGENCY study was included as a category 3 study in the RMP.

2.2.2. Ecotoxicity/environmental risk assessment

Obinutuzumab is a monoclonal antibody that does not incorporate any non-natural amino acids. Hence, it is considered a natural protein expected to be readily degraded. Therefore, obinutuzumab is not expected to pose a significant risk to the environment in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*).

2.2.3. Discussion on non-clinical aspects

Obinutuzumab is a recombinant, humanised immunoglobulin IgG1 mAb designed to selectively target $CD20^+$ B-cells which does not cross-react with rodent CD20 molecules, precluding the conduct of traditional carcinogenicity studies. In line with ICH guideline S6(R1) and based on a weight of evidence approach, it was concluded that a 2-year rodent carcinogenicity study with obinutuzumab is not warranted in the lupus nephritis indication. Long term safety in LN patients was included in the RMP as missing information. The long-term part of the REGENCY study was included as a category 3 study in the RMP.

2.2.4. Conclusion on the non-clinical aspects

Obinutuzumab is not expected to pose a risk to the environment.

The non-clinical data package of obinutuzumab in oncology indications was considered adequate to support the extension of indication in lupus nephritis. In line with ICH guideline S6(R1) and based on a weight of evidence approach, the CHMP concluded that a 2-year rodent carcinogenicity study with obinutuzumab is not warranted to support the lupus nephritis extension of indication.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the EU were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 Summary of studies contributing to PK and PD evaluation

Study Number	Study Design	Population	No. of Patients Evaluable for PK	No. of Patients Evaluable for PD	No. of Patients Evaluable for Immunogenicity[a]	Dose, Route, and Regimen
WA29748 (NOBILITY)	Phase II, randomized, double-blind, placebo-controlled, multicenter study evaluated the safety and efficacy of obinutuzumab + MMF/MPA vs. placebo + MMF/MPA	Adult patients with ISN/RPS 2003 Class III or IV lupus nephritis with or without concomitant Class V lupus nephritis (proliferative lupus nephritis) treated with SoC [b]	63	61	63 [c]	Standard rate infusions 1000 mg on Day 1 and Weeks, 2, 24 and 26.
CA41705 (REGENCY)	Phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of obinutuzumab + MMF vs. placebo + MMF	Adult patients aged 18-75 with ISN/RPS 2003 Class III or IV lupus nephritis with or without concomitant Class V lupus nephritis (proliferative lupus nephritis) treated with SoC [d]	134	136	136	Standard rate infusions Arm 1: 1000 mg on Day 1 and Weeks, 2, 24, 26, 50 and 52. (2-2-2 Regimen) Arm 2: 1000 mg on Day 1 and Weeks 2, 24, 26 and 52 (2-2-1 Regimen) Patients with an adequate response at Week 76 continued blinded infusions at Week 80 and every 6 months thereafter. Those with an inadequate response/ some improvement from baseline were eligible for OLT. OLT follows the initial obinutuzumab treatment schedule with infusions on OLT Day 1; at OLT Weeks 2, 24, 26, 52 and every 6 months thereafter.

ISN=International Society of Nephrology; MMF= mycophenolate mofetil; MPA=Mycophenolic acid; OLT= Open-label treatment; RPS=Renal Pathology Society; SoC= Standard-of-care.

[a] The immunogenicity population is the same as the safety-evaluable population.

[b] In NOBILITY, standard of care included therapy with MMF and corticosteroids, tapered to prednisone equivalent 7.5 mg/day by Week 12 and maintained at this dose until Week 52.

[c] One patient had a sample assayed in error and was not included in the immunogenicity analysis (details provided in 5.3.5.3 Integrated Summary of Immunogenicity, Section 5.1.1).

[d] In REGENCY, standard of care included therapy with MMF and corticosteroids, tapered to prednisone equivalent 5 mg/day by Week 24 and maintained at this dose until Week 80.

2.3.2. Pharmacokinetics

The PK-evaluable population included all participants in the NOBILITY and REGENCY studies who were randomised to and received any dose of obinutuzumab given as study medication, had at least one post-dose PK sample that is evaluable and had no major protocol deviations that would impact the PK results.

B cell depletion was determined in both the NOBILITY and REGENCY studies using two assays: a conventional flow cytometry (TBNK) with a defined threshold of 10 cells/µL, and an additional high sensitivity flow cytometry (HSFC) assay, MRB1.1, with a lower limit of quantitation of 0.441 cells/µL of blood.

The immunogenicity population was the same as the safety–evaluable population in the NOBILITY and REGENCY studies, which was defined as patients who received any part of blinded infusion of obinutuzumab or placebo.

PK assay

Concentrations of obinutuzumab in human serum samples from the NOBILITY and REGENCY studies were measured using a validated enzyme-linked immunosorbent assay (ELISA) method with a lower limit of quantification (LLOQ) of 4.05 ng/mL in human serum. :

- For the NOBILITY study, final bioanalytical data are reported in two bioanalytical reports (BARs): Partial Report No.1 covering samples analyzed between 6 July 2017 and 26 March 2019 and Partial Report No. 2 covering samples analyzed between 4 November 2019 and 4 October 2023.
- For the REGENCY study, bioanalytical data are presented in two BARs: Partial Report No. 1 covering samples analyzed between 23 July 2021 and 9 July 2024 and Partial Report No.2 covering samples analyzed between 19 August 2024 and 22 August 2024.

ADA assay

Anti-obinutuzumab antibodies (ADAs) were assessed in serum samples using a validated ELISA method with in-study validation performed according to the draft FDA Guidance for Industry on Immunogenicity testing (U.S. Food and Drug Administration 2019, Shankar et al. 2008[29]). Sample testing was conducted using a tiered approach consisting of a primary screening assay (tier 1), a confirmatory assay (tier 2) and a titration step (tier 3) if applicable. Details of the methods and assay performance for the determination of ADAs are provided in the BARs for both studies:

- For the NOBILITY study final bioanalytical data reporting for ADAs are presented in two BARs: Partial Report No.1 covering samples analyzed between 6 July 2017 and 19 March 2019 and Partial Report No. 2 covering samples analyzed between 28 January 2020 and 10 October 2023.
- For the REGENCY study bioanalytical data reporting for ADAs are presented in two BARs: Partial Report No. 1 covering samples analyzed between 06 January 2022 and 9 July 2024 and Partial Report No.2 covering samples analyzed between 21 August 2024 and 28 August 2024 REGENCY.

Pop PK modelling

The Pop PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software. The FOCEI option was used for all model runs.

The Pop PK population of obinutuzumab in patients with proliferative lupus nephritis (ISN/RPS 2003 class III/IV) included data from Phase 2 Study WA29748 (NOBILITY) and Phase 3 Study CA41705 (REGENCY). A total of 3326 samples from 196 predominately female patients (85.2%) were included. A total of 177

[29] Shankar, G.; Devanarayan, V. et al, Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. J Pharm Biomed Anal 2008.48 (5):1267-81.

(5.3%) post-dose BLQ samples were excluded in addition to 19 and 28 quantifiable pre- and post-dose samples, respectively, with PK observations incompatible with the individual concentration-time profiles.

Figure 1 Summary of data used in the analysis

Study	Number of Patients	Number of All Post-dose Observations	Included	Excluded		
				Post-dose positive	Post-dose BLQ	Pre-dose positive
Total	196	3531	3326	28 (0.8%)	177 (5.3%)	19
WA29748	62	787	647	7 (1.1%)	133 (20.6%)	7
CA41705	134	2744	2679	21 (0.8%)	44 (1.6%)	12

[a] Three patients (ID 1105 from NOBILITY, and ID 50032, and 50216 from REGENCY) did not have any evaluable PK samples and were excluded from the analysis. One placebo arm patient (1107) was administered obinutuzumab dose during the blinded period, had 9 quantifiable observations, but was not included in the analysis. Placebo patients who got obinutuzumab doses during the open-label period were not included in the analysis.

The base Pop PK model was a linear two-compartment model parameterised in terms of clearance (CL), central volume (Vc), inter-compartment clearance (Q), and peripheral volume (Vp). Clearance was split into a linear part expressed as a sum of steady-state clearance (CLINF) and a non-linear time-dependent part (CLT = CLT0·exp(-kdes·t)), where CLT0 is the initial value of time-dependent clearance, kdes is the rate of decay of the time-dependent clearance, and t is time after the first dose. Inter-individual random effects were included on CL, Vc and on the residual error. An exponential intra-individual error model was implemented in the log-transformed concentration scale to describe the residuals. Effects of body weight on CLT0, CLinf, Vc and Vp were included by allometric scaling with estimated exponents.

The following covariates were planned for evaluation using a stepwise approach with forward inclusion followed by back-ward exclusion: effects of sex and race on CLINF and Vc, effects of age, presence of ADAs, renal function (UPCR), albumin, IgG, and ISN/RPS LN class on CLT0 and CLINF. Only effects of weight; albumin on CLT0 and CLinf; IgG on CLinf; UPCR on CLT0 and sex on Vc were retained in the final model (Model 009). Effects of CRCLN on CLT0 and methylprednisolone on CLinf were tested in later runs and rejected.

The parameters of the final model (Model 009) were dependent on baseline albumin, IgG concentrations and UPCR which all change with time in the LN population, as they depend on the patient's condition that may change during treatment. A sensitivity test including time varying rather than baseline values of these covariates improved the OFV (Model 013). Overall, there were no advantages of using the more complex model and Model 009 remained the final model. Parameter estimates of the final model are listed in Table 2. Parameter estimates were evaluated by bootstrap analysis (n=1000) with 83.7% of runs converging.

Table 2 Parameters estimates of the final model 009

Fixed Effect Parameter		Estimate	RSE (%)	95%CI
k_{des} (1/day)	θ_1	0.0106	8.22	0.00892 ; 0.0123
CL_{T0} (L/day)	θ_2	0.0923	5.18	0.083 ; 0.102
CL_{INF} (L/day)	θ_3	0.125	4.07	0.115 ; 0.134
V_c (L)	θ_4	2.22	1.9	2.14 ; 2.3
V_p (L)	θ_5	1.60	5.38	1.43 ; 1.76
Q (L/day)	θ_6	0.602	22.9	0.331 ; 0.873
CL_{T0}, CL_{INF} ~ WT	θ_7	0.708	17.6	0.465 ; 0.952
V_c ~ WT	θ_8	0.480	14.3	0.345 ; 0.614
V_p ~ WT	θ_9	0.906	8.92	0.748 ; 1.06
SDL	θ_{10}	0.891	5.42	0.796 ; 0.986
SDH	θ_{11}	0.171	3.02	0.161 ; 0.181
SD_{50} (µg/mL)	θ_{12}	1.53	14.2	1.1 ; 1.95
CL_{T0} ~ ALB	θ_{13}	-2.09	10.6	-2.52 ; -1.65
CL_{T0} ~ UPCR	θ_{14}	0.235	19.9	0.143 ; 0.327
CL_{INF} ~ ALB	θ_{15}	-0.491	26.9	-0.75 ; -0.232
CL_{INF} ~ IgG	θ_{16}	0.234	22.8	0.13 ; 0.339
V_c ~ SEX	θ_{17}	1.15	3.8	1.06 ; 1.23

Variance Parameter		Estimate	RSE (%)	95%CI	Variability	Shrinkage
ω^2_{kdes}	Ω(1,1)	0.664	17.6	0.435 ; 0.893	CV=81.5%	16.8%
ω^2_{CLT0}	Ω(2,2)	0.144	17.8	0.0936 ; 0.194	CV=37.9%	18.7%
ω^2_{CLINF}	Ω(3,3)	0.0941	9.69	0.0762 ; 0.112	CV=30.7%	1.4%
ω^2_{Vc}	Ω(4,4)	0.0205	15.1	0.0145 ; 0.0266	CV=14.3%	8.6%
$\omega^2\varepsilon$	Ω(5,5)	0.0679	15.5	0.0473 ; 0.0885	CV=26.1%	4.8%
σ^2	Σ(1,1)	1	FIXED			3.5%

Source: 009ParEst.csv

SE: standard error; RSE: relative standard error.
%RSE=100·SE/PE, where PE is a parameter estimate.
95% CI: 95% confidence interval.
SD: standard deviation; CV: coefficient of variation, CV = 100*SD %.

The final model for obinutuzumab LN was evaluated by GoF, NPDE and pcVC plots as depicted in Figure 2, Figure 3, Figure 4, Figure 5 and Figure 6.

Figure 2 Goodness of fit for the final model 009

DV: observed concentrations; PRED: population predictions of the model.
IPRED: individual predictions of the model; CWRES: conditional weighted residuals.
IWRES: individual weighted residuals; TIME: time after the first dose.
The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.

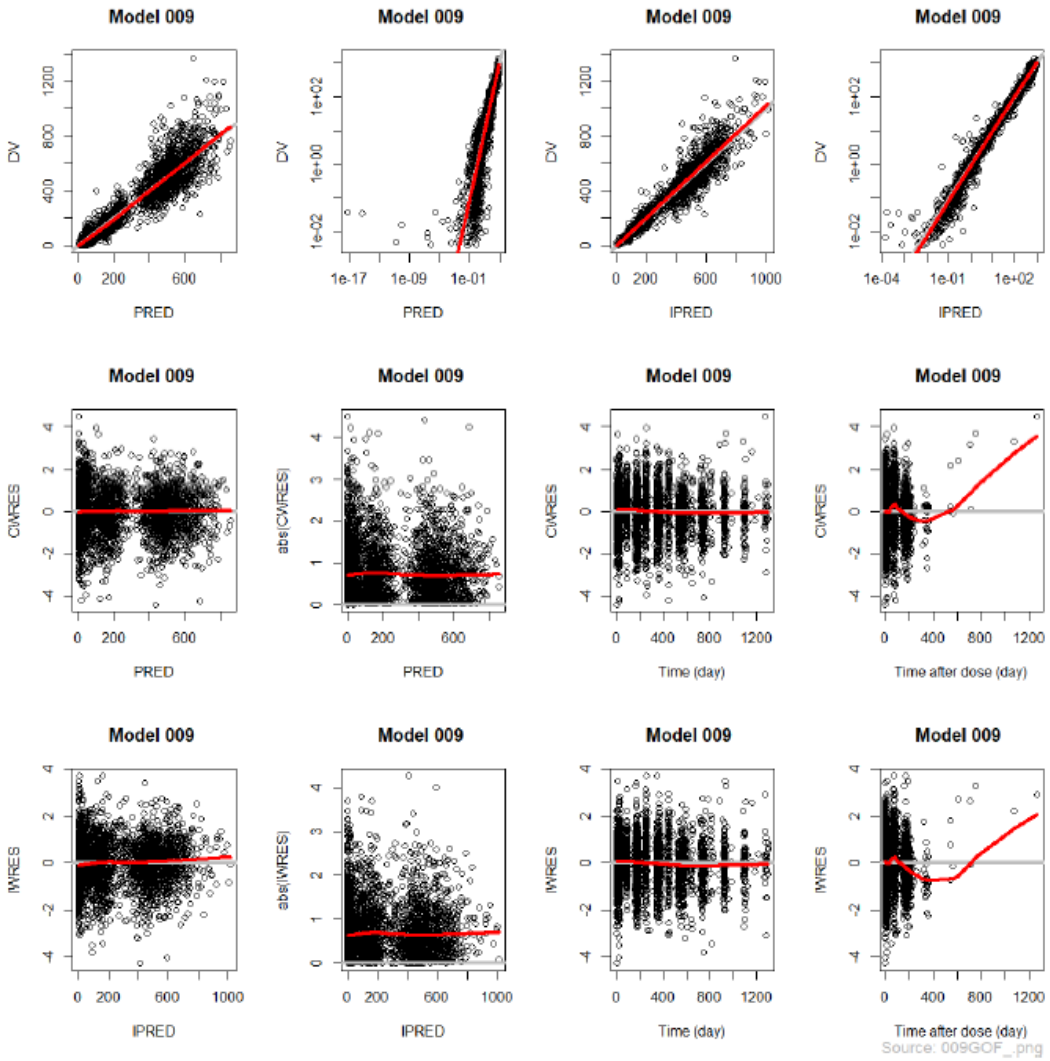


Figure 3 NPDE versus time, time after dose, population predictions and covariates, final model 009

Top and Middle Rows: Circles correspond to NPDE of observations in the distribution of 1000 simulated values. Lines at y=0 correspond to median, and dashed lines show the 10th and 90th percentiles. Red lines show the lowess trend lines. Bottom Row: NPDE values are plotted versus categorical covariates using box and whisker plots. Median values are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles. Lines at y=0 correspond to expected medians, and dashed lines show the expected 10th and 90th percentiles.

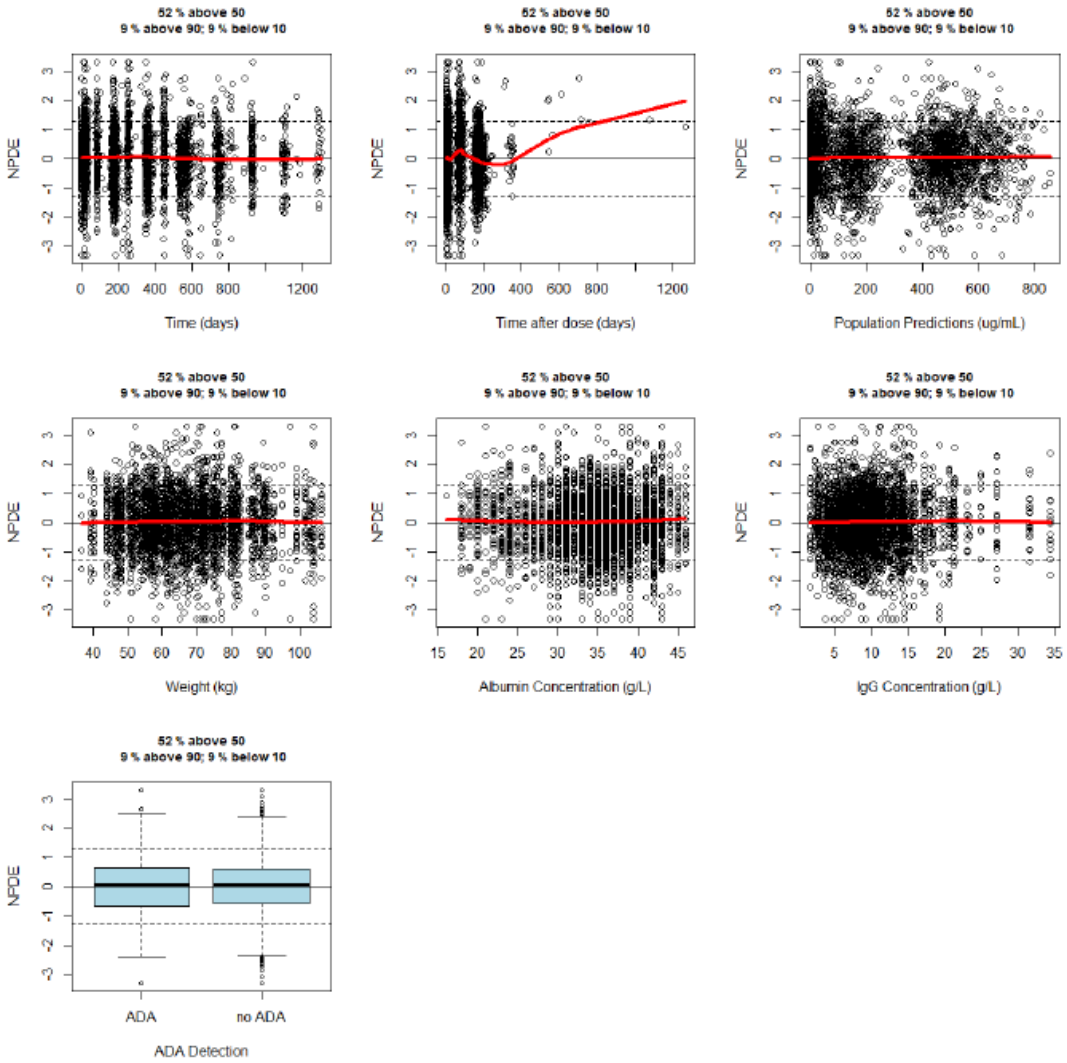
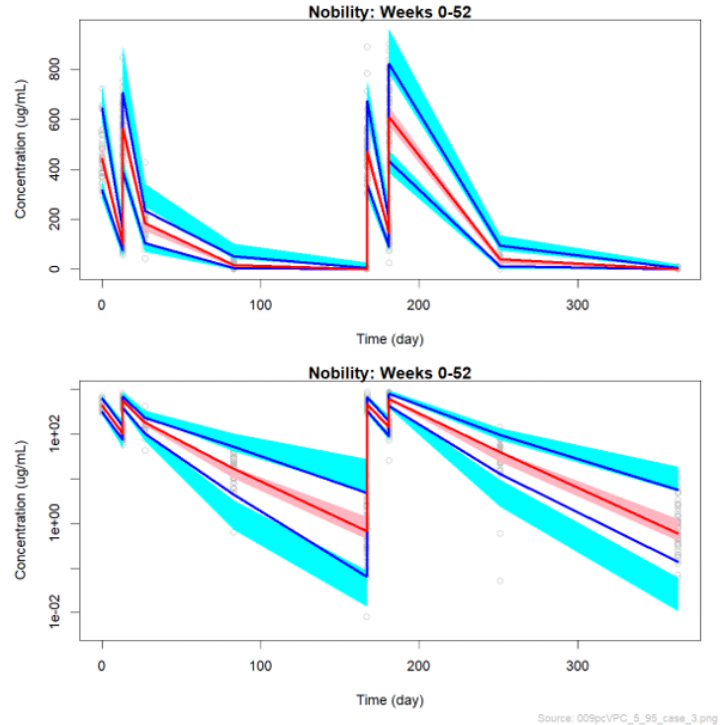
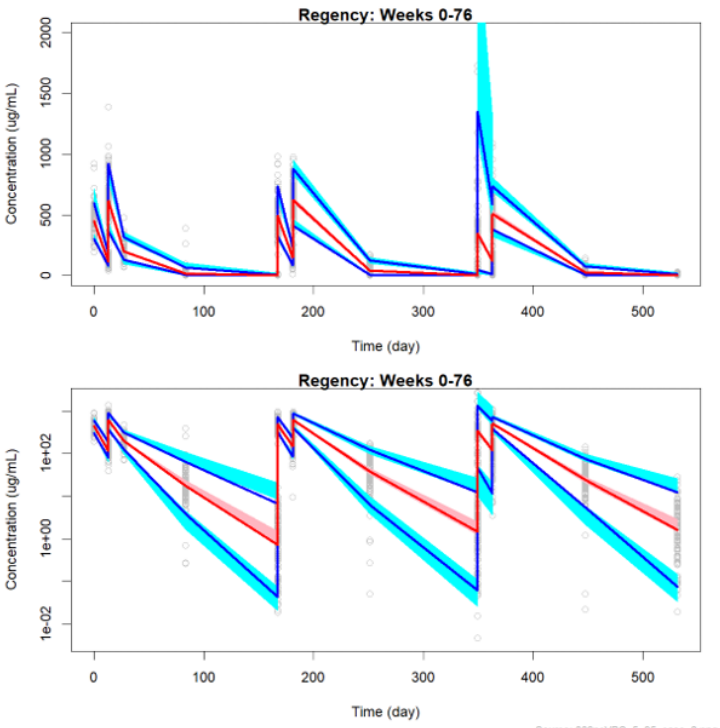


Figure 4 ***Prediction-Corrected Visual Predictive Check, Final Model 009: NOBILITY Study, Weeks 0-52***



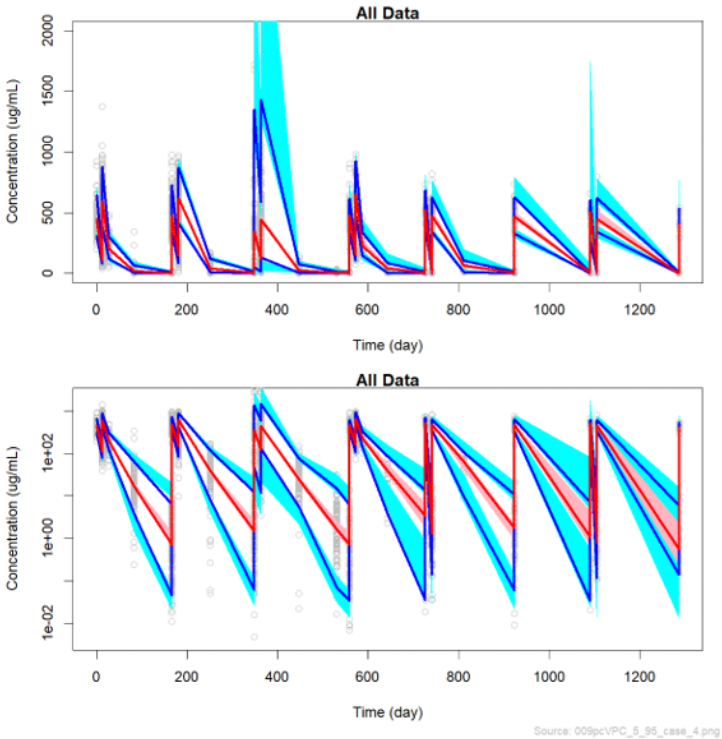
The circles show observed data. The lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations. The shaded regions show 90% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 1000 trials with dosing, sampling, and the covariate values of the analysis data set.

Figure 5 ***Prediction-Corrected Visual Predictive Check, Final Model 009: REGENCY Study, Weeks 0-76***



The circles show observed data. The lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations. The shaded regions show 90% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 1000 trials with dosing, sampling, and the covariate values of the analysis data set.

Figure 6 ***Prediction-Corrected Visual Predictive Check, Final Model 009: All Data***



Source: 009pcVPC_5_95_case_4.png

The circles show observed data. The lines show median (red), and the 5th and 95th percentiles (blue) of the observed concentrations. The shaded regions show 90% confidence intervals on these quantities obtained by simulations. The simulated values were computed from 1000 trials with dosing, sampling, and the covariate values of the analysis data set.

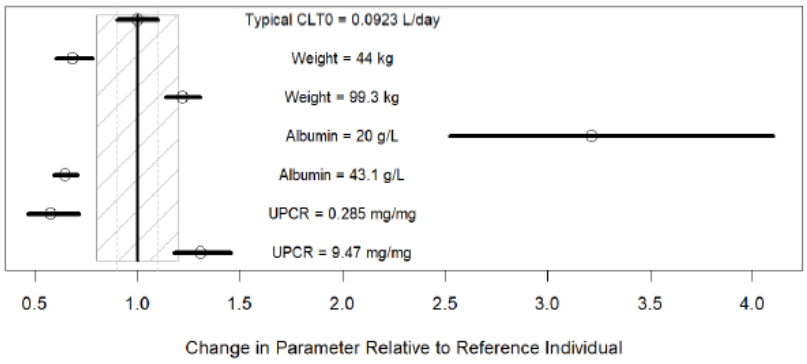
Covariate effects

Conditional simulations were performed to investigate the effects of covariates. The influence of included covariates on clearance is illustrated in Figure 7.

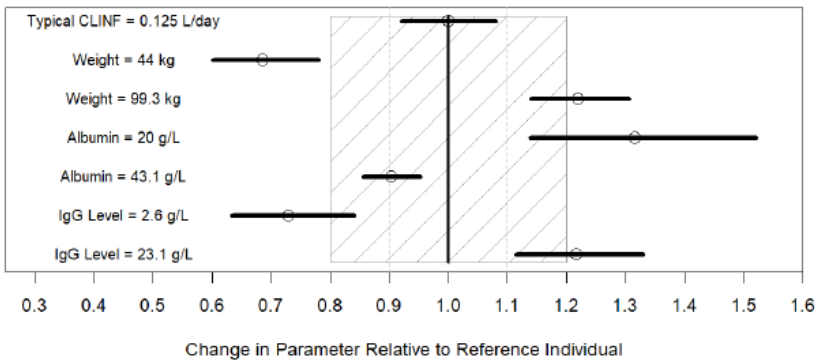
Figure 7 Covariate effects on obinutuzmab clearance, final model 009

The ratio of the typical parameter and its 95% CI for subpopulations to the typical parameter of a reference patient is illustrated. For categorical covariates and for continuous covariates with a specific value, point estimates are represented by open circles, and 95% CIs are represented by horizontal bars. The hatched area represents a typical value ± 20%. The values of the continuous covariates represent 2.5th and 97.5th percentiles of the values in the analysis data set.

Covariate Effects on Initial Value Of Time-Dependent Clearance (CLT0)
Reference: Weight = 75 kg; Albumin = 35 g/L; UPCR = 35 mg/mg



Covariate Effects on Steady State Clearance (CLINF)
Reference: Weight = 75 kg; Albumin = 35 g/L; IgG Level = 10 g/L



The population pharmacokinetic analysis (n = 196) showed that creatinine clearance does not affect the pharmacokinetics of obinutuzumab in patients with LN. The pharmacokinetics of obinutuzumab in patients with mild (CrCl 60 - <90 mL/min, n=45) or moderate (CrCl 30 - <60 mL/min, n=17) renal impairment were similar to those in patients with normal kidney function.

Simulations

The Pop PK model for obinutuzumab LN was used for several simulation studies. Individual PK parameters were estimated from the final model.

Exposure following five doses at Day 0, 14, 168, 182 and 364 was simulated and compared to exposure following six doses as applied in Regency.

The Recency study which investigated two dose regimens, is not powered to show benefit of 6 doses over 5, thus clinical trial simulations were conducted to evaluate whether a larger clinical trial would be able to demonstrate clinically significant difference between the two regimens with regard to CRR.

Effect of short duration infusion (SDI, 1.5 hour) versus standard infusion (4.25/3.25 hour) was simulated using the 5-dose regimen with regard to exposure Cmax and AUC and the relation to safety measure IRR.

Please refer to the PK/PD Section 2.3.4. for further results.

Pharmacokinetics in the target population using Non-compartmental Analysis

Nobility study WA29748

After screening, eligible patients were randomized in a 1:1 ratio to receive either obinutuzumab 1000 mg (administered as an absolute [flat] dose by IV infusion on Days 1, 15, 168, and 182) or placebo (infused in the same volume and on the same scheduled days as active treatment).

Concentrations of obinutuzumab were measured in serum from sparse blood samples collected pre-infusion (within 30 minutes prior to the start of infusion) and at the end of infusion (within 30 minutes after the end of infusion) on Day 1, Weeks 2, 24 and 26. In addition, a single blood sample for the measurement of serum obinutuzumab concentrations was collected at Weeks 4, 12, 36 and 52 or early termination visit. Blood samples were collected for assessment of ADAs at Day 1 (prior to the first obinutuzumab infusion) and at Weeks 24 and 52 or early termination visit. In addition, blood samples were collected throughout the study for the assessment of biomarkers in plasma and serum, for the quantitative assessment of Ig levels, and for flow cytometry.

A non-compartmental analysis (NCA) of PK data from the NOBILITY study has been performed.

The PK-evaluable population consisted of 63 patients in the obinutuzumab arm who received any dose of obinutuzumab as study medication and had at least one evaluable post-dose PK sample. The PK dataset contained data from 54 (87.1%) female and 8 (12.9%) male patients. Median (range) body weight and age of the population were 66.8 kg (44 to 104 kg) and 32 years (18 to 59 years), respectively. Median and individual serum obinutuzumab concentration-time profiles in patients with lupus nephritis in the NOBILITY study are shown in Figure 8. Obinutuzumab serum-concentration data up to Week 52 were analyzed using NCA in the PK-evaluable patient population. The analyses were conducted to provide exposure estimates (C_{max}, AUC, and C_{trough}) for Weeks 0 to 24, Weeks 24 to 52, and an assessment of cumulative exposure up to Week 52. Because sparse sampling was used throughout the study, NCA analyses could not be performed for all PK-evaluable patients due to missing PK samples or limited collection of PK samples. In addition, patients who had dose deviations (including a missing dose and/or dose reduction) were excluded from the NCA analysis. The actual number of patients for whom PK parameters were derived using NCA is presented in Table 3.

Median serum obinutuzumab C_{max} and trough concentrations (C_{trough}) increased over the course of treatment. Geometric mean C_{trough} values reached steady state by Week 52 (Figure 1 and Table 3).

Figure 8 Median and Individual Patient Serum-Concentration Profiles following Obinutuzumab 1000 mg administration on Day 1, Weeks 2, 24 and 26 in the NOBILITY Study (Log-Linear Scale)

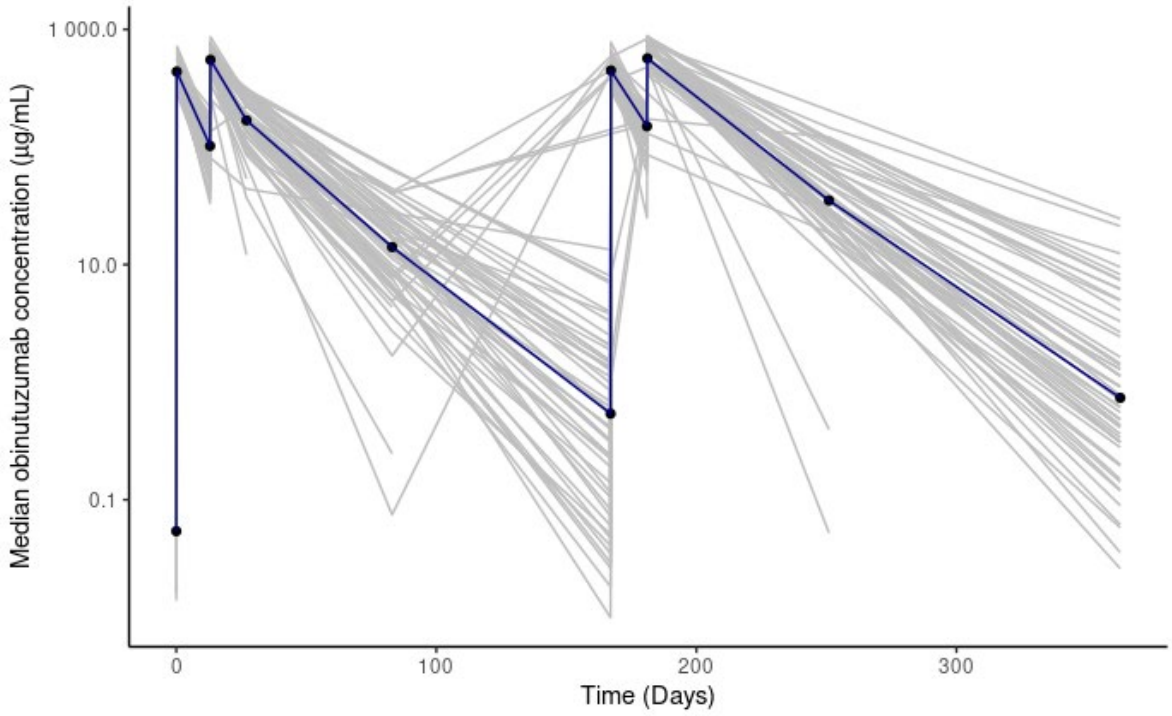


Table 3 Summary statistics of PK parameters derived by NCA following administration of obinutuzumab on day 1, Weeks 2, 24 and 26 in the NOBILITY study (PK-evaluable population)

Timepoint	PK Parameter	Arithmetic Mean (SD)	Median (Range)	Geo. Mean (CV)	n
Week $_{0-24}$	C_{max} (µg/mL)[a]	553	554	535	42
		(138)	(221-862)	(28.2)	
	C_{trough} (µg/mL)	1.21	0.408	0.355	42
		(1.95)	(0.00995-7.98)	(472)	
	AUC_{0-24} (µg/mL*day)	16,100	14,300	15,300	42
		(5180)	(9,340-33,000)	(30.8)	
Week $_{24-52}$	C_{max} (µg/mL) [a]	596	563	549	48
		(169)	(27.5-885)	(58.0)	
	C_{trough} (µg/mL)	2.36	0.616	0.733	48
		(4.25)	(0.026-24.5)	(355)	
	AUC_{24-52} (µg/mL*day)	31,900	29,500	29,800	47
		(12,900)	(7,240-75,600)	(38.9)	
Week $_{0-52}$	AUC_{0-52} (µg/mL*day)	47,900	43,600	46,100	36
		(14,700)	(32,300-94,200)	(27.1)	

AUC = area under the concentration-time curve; C_{max} = maximum serum concentration; C_{trough} = trough concentration; CV = coefficient of variation; n = number of patients with evaluable data; NCA = non-compartmental analysis; PK = pharmacokinetic; SD = standard deviation

[a] Reported C_{max} following the second dose of the 2-week dosing interval.

NCA analyses could not be performed for all patients due to missing samples or limited sample collection. Patients with dose deviations (missing dose and/or dose reduction) were also excluded from NCA analysis

In the mITT population, by HSFC, at Week 2, (90% vs. 2.0%) of patients were BLOQ of HSFC (<0.441 cell/mcL); at Week 4 – (89.3% vs.2.1%, at Week 12 – (90.6% vs.3.6%), at Week 24 (72.2% vs. 4.3%), at Week 52 (79.6% vs.0%) and at Week 104 (8.2% vs.2.4%) of patients were BLOQ in the obi+MMF arm vs. placebo+MMF arm respectively. By HSFC, mean values of CD19+ cells at Week 104 were 159.94 cells/μL in the obi+MMF arm and 184.48 cells/μL in the placebo+MMF arm.

REGENCY Study CA41705

After screening, eligible patients were randomized to receive obinutuzumab or placebo in a 1:1 ratio. Patients randomized to receive obinutuzumab were further randomized in a 1:1 ratio to receive one of the two obinutuzumab dosing schedules:

- Obinutuzumab Arm 1 (2-2-2 Regimen): absolute (flat) dose of 1000 mg IV infusion on Day 1 and Weeks 2, 24, 26, 50, and 52
- Obinutuzumab Arm 2 (2-2-1 Regimen): absolute (flat) dose of 1000 mg IV infusion on Day 1 and Weeks 2, 24, 26, and 52

Placebo was administered at the same volume and on the same scheduled days in the control arm.

Up to the time of the primary efficacy endpoint at Week 76, concentrations of obinutuzumab were measured in serum from sparse blood samples collected pre infusion (within 30 minutes prior to the start of infusion) and at the end of infusion (within 30 minutes after the end of infusion) on Day 1, Weeks 2, 24, 26, 50 and 52. In addition, a single blood sample for the measurement of serum obinutuzumab concentrations was collected at Weeks 4, 12, 36, 64 and 76 or early termination visit. Blood samples were collected for assessment of ADAs at Day 1 (prior to the first study drug infusion) and at Weeks 2, 4, 12, 24, 36, 50 and 76 or early termination visit.

For patients who continued blinded treatment after Week 76, concentrations of obinutuzumab were measured in serum from sparse blood samples collected at Weeks 80, 106, 132, 158, 184 and every 6 months thereafter. At infusion visits, samples were collected pre-infusion (within 30 minutes prior to the start of infusion) and at the end of infusion (within 30 minutes after the end of infusion). On non-infusion visits a single sample was collected. Blood samples for ADA assessments were collected at Weeks 80, 106, 132, 158, 184 and every 6 months thereafter.

Up to the time of the primary efficacy endpoint at Week 76, concentrations of obinutuzumab were measured in serum from sparse blood samples collected pre infusion (within 30 minutes prior to the start of infusion) and at the end of infusion (within 30 minutes after the end of infusion) on Day 1, Weeks 2, 24, 26, 50 and 52. In addition, a single blood sample for the measurement of serum obinutuzumab concentrations was collected at Weeks 4, 12, 36, 64 and 76 or early termination visit. Blood samples were collected for assessment of ADAs at Day 1 (prior to the first study drug infusion) and at Weeks 2, 4, 12, 24, 36, 50 and 76 or early termination visit.

For patients who continued blinded treatment after Week 76, concentrations of obinutuzumab were measured in serum from sparse blood samples collected at Weeks 80, 106, 132, 158, 184 and every 6 months thereafter. At infusion visits, samples were collected pre-infusion (within 30 minutes prior to the start of infusion) and at the end of infusion (within 30 minutes after the end of infusion). On non-infusion

visits, a single sample was collected. Blood samples for ADA assessments were collected at Weeks 80, 106, 132, 158, 184 and every 6 months thereafter.

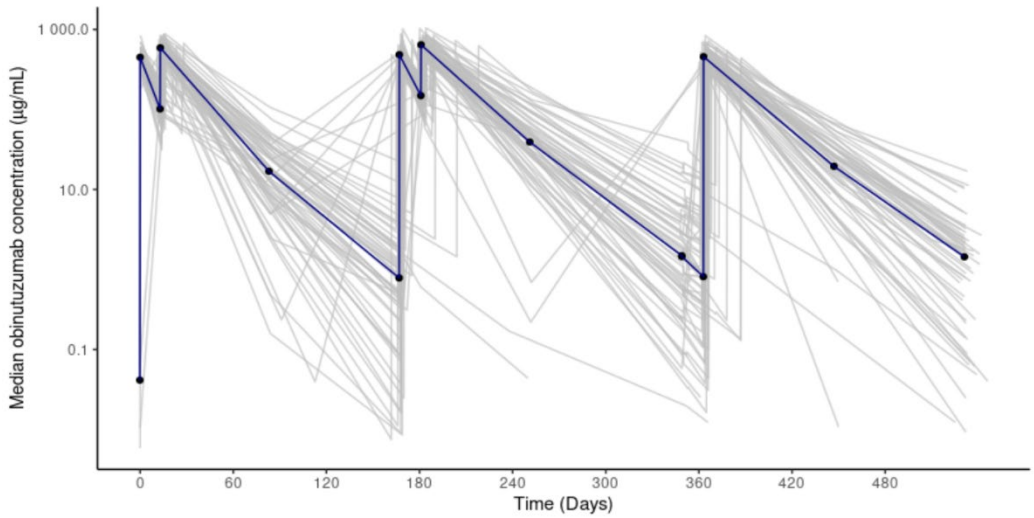
A non-compartmental analysis (NCA) of PK data from the NOBILITY study has been performed.

The PK-evaluable population consisted of 134 patients, 68 patients who received the 2 2-2 regimen and 66 patients who received the 2-2-1 regimen. Obinutuzumab serum concentration data up to Week 76 were analyzed using NCA in the PK-evaluable patient population. The analyses were conducted to provide exposure estimates (C_{max}, AUC, and C_{trough}) for Weeks 0 to 24, Weeks 24 to 52, Weeks 52 to 76, and an assessment of cumulative exposure up to Week 76. Because sparse sampling was used throughout the study, NCA analyses could not be performed for all PK-evaluable patients due to missing PK samples or limited collection of PK samples. In addition, patients who had dose deviations (including a missing dose and/or dose reduction) were excluded from the NCA analysis. The actual number of patients for whom PK parameters were derived using NCA is presented for each dose arm in Table 4.

The median and individual patient obinutuzumab concentration-time data over the course of treatment up to Week 76 in patients with lupus nephritis (2-2-1 and 2-2-2 regimens, respectively) are presented in Figure 9 and Figure 10.

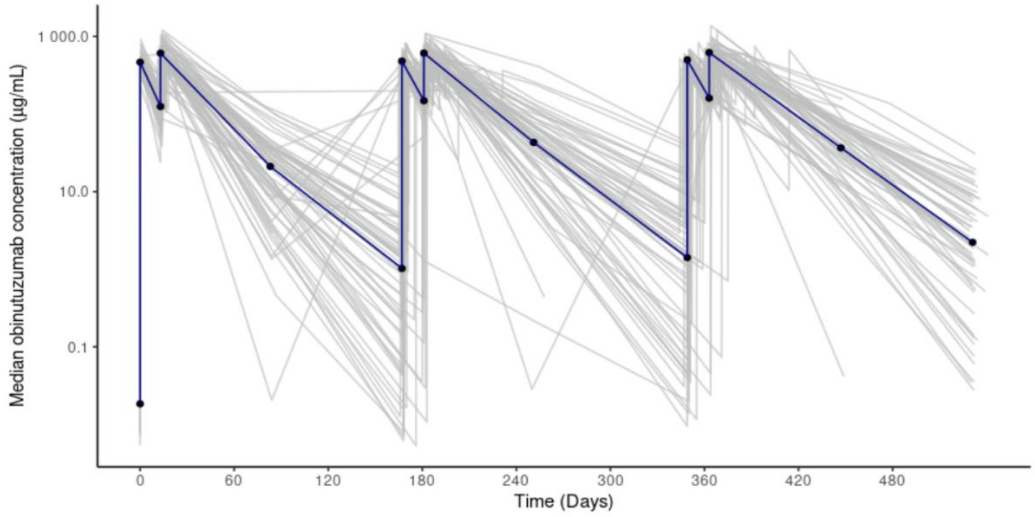
Following two 1000 mg infusions, administered at 2-week intervals every 6 months for the first 2 courses, comparable Cmax were observed from Week0-24 to Week0-52 following two 1000 mg infusions of obinutuzumab administered at 2-week intervals every 6 months (Figure 9). Systemic exposure (AUC) increased with time from Week0-24 to Week24-52 (2-2-1 regimen) or Week24-50 (2-2-2 regimen) (Table 4). In the 2-2-2 regimen, AUC24-50 and AUC50-76 were comparable (Figure 9). Cumulative AUC0-76 in the 2-2-2 dosing regimen was approximately 19% higher (88,600 µg/mL*day) compared with the 2-2-1 dosing regimen (74,400 µg/mL*day) (Figure 9); however, a high overlap in systemic exposures was observed between the two dosing regimens (Figure 9, Figure 10 and Figure 9).

Figure 9 Median and Individual Patient Serum-Concentration Profiles of Obinutuzumab following 2-2-1 Dosing Regimen in the REGENCY Study (PK-Evaluable Population; Log-Linear Scale)



SE = standard error; PK = pharmacokinetic

Figure 10 Median and Individual Patient Serum-Concentration Profiles of Obinutuzumab following 2-2-2 Dosing Regimen Regimen in the REGENCY Study (PK-Evaluable Population; Log-Linear Scale)



SE = standard error; PK = pharmacokinetic

Figure 11 Summary Statistics of PK Parameters Derived by NCA following 2-2-1 and 2.2.2 Dosing Regimen in the REGENCY Study (PK-Evaluable Population)

Timepoint	PK Parameter	Arithmetic Mean (SD)	Median (Range)	Geo. Mean (CV)	n
2-2-1 Dosing Regimen					
Week $_{0-24}$	C_{max} (µg/mL)[a]	560 (194)	577 (149–885)	518 (45.3)	44
	C_{trough} (µg/mL)	1.78 (3.82)	0.496 (0.0075–22)	0.402 (761)	44
	AUC_{0-24} (µg/mL*day)	16,400 (5,600)	15,000 (6810–32,200)	15,600 (33.7)	43
Week $_{24-52}$	C_{max} (µg/mL) [a]	661 (144)	655 (440–1040)	646 (21.7)	52
	C_{trough} (µg/mL)	13 (75)	0.813 (0.0163–543)	0.91 (752)	52
	AUC_{24-52} (µg/mL*day)	32,800 (7,920)	31,300 (22,000–61,800)	31,900 (23.2)	52
Week $_{0-52}$	AUC_{0-52} (µg/mL*day) [b]	50,800 (11,500)	47300 (30,600–78,700)	49,600 (22.2)	39
Week $_{52-76}$	C_{max} (µg/mL)	482 (117)	460 (288–838)	469 (23.8)	50
	C_{trough} (µg/mL)	2.45 (3.44)	1.47 (0.00924–16.9)	0.942 (396)	50
	AUC_{52-76} (µg/mL*day)	23,000 (6,820)	21,000 (11,300–44,600)	22,100 (28.4)	50
Week $_{0-76}$	AUC_{0-76} (µg/mL*day)	74,400 (15,400)	70,600 (46,000–117,000)	72,900 (20.6)	36
2-2-2 Dosing Regimen					
Week $_{0-24}$	C_{max} (µg/mL) [a]	632 (215)	610 (142-1,210)	589 (43.3)	56

Timepoint	PK Parameter	Arithmetic Mean (SD)	Median (Range)	Geo. Mean (CV)	n
	C_{trough} (µg/mL)	2.65 (4.23)	1.22 (0.00528-20.3)	0.568 (1,350)	56
	AUC_{0-24} (µg/mL*day)	19,400 (6,610)	18,200 (9,120-40,100)	18,400 (34)	53
Week $_{24-50}$	C_{max} (µg/mL) [a]	649 (159)	624 (367-1,090)	631 (24.1)	54
	C_{trough} (µg/mL)	5.57 (9.3)	1.62 (0.00947-40.1)	1.12 (1,300)	54
	AUC_{24-50} (µg/mL*day)	32,600 (10,400)	30,400 (19,600-82,900)	31,300 (27)	54
Week $_{0-50}$	AUC_{0-50} (µg/mL*day) [b]	52,500 (17,100)	49,800 (32,100-123,000)	50,300 (28.6)	46
Week $_{50-76}$	C_{max} (µg/mL) [a]	645 (155)	619 (423-1,200)	575 (75.4)	46
	C_{trough} (µg/mL)	4.68 (6.16)	2.16 (0.0272-30.7)	1.67 (520)	46
	AUC_{50-76} (µg/mL*day)	35,300 (9,460)	33,500 (22,300-62,800)	32,900 (40.4)	46
Week $_{0-76}$	AUC_{0-76} (µg/mL*day)	88,600 (26,100)	81,500 (57,500-180,000)	85,500 (26.7)	35

AUC = area under the concentration-time curve; C_{max} = maximum serum concentration; C_{trough} = trough concentration; CV = coefficient of variation; n = number of patients with evaluable data; NCA = non-compartmental analysis; PK = pharmacokinetic; SD = standard deviation.

[a] Reported C_{max} following the second dose of the 2-week dosing interval.

[b] Only patients who had measurable AUC1 and AUC2 were considered for reporting AUC_{0-52} or AUC_{0-50}

NCA analyses could not be performed for all patients due to missing samples or limited sample collection. Patients with dose deviations (missing dose and/or dose reduction) were also excluded from NCA analysis, and patients who did not deviate more than 10% dosing error were only considered for AUC estimation.

PopPK Simulations

The predicted exposure parameters (Cmax and AUC) obtained from popPK simulations (Figure 12) aligned with observed exposure parameters from NCA analysis of the REGENCY data for the 2-2-1 dosing regimen. A difference was observed between the NCA derived AUC0-76 and the predicted AUC0-76 derived using popPK due to the limited number of patients (n = 36) that could be used for NCA estimations. The predicted exposure parameters (Cmax and AUC) were also maintained at steady state (Figure 13).

Figure 12 Predicted Obinutuzumab PK Parameters for the 2-2-1 Dosing Regimen using the Integrated popPK Model

Timepoint	PK Parameter	Statistic	
		Arithmetic Mean (SD)	Median (Range)
Week$_{0-24}$	C_{max} µg/mL	582 (106)	580 (375-935)
	AUC µg/mL*day	11,200 (4,550)	10,400 (2,440-29,000)
Week$_{24-50}$	C_{max} µg/mL	626 (112)	623 (407-995)

Timepoint	PK Parameter	Statistic	
$Week_{0-50}$	AUC µg/mL*day	27,700 (10,300)	26,100 (7,620-68,400)
$Week_{50-76}$	C_{max} µg/mL	471 (81.7)	472 (293-713)
$Week_{0-76}$	AUC µg/mL*day	36,800 (13,800)	34,600 (11,000-89,200)

AUC = area under the concentration-time curve; C_{max} = maximum observed serum concentration; SD = standard deviation.

Figure 13 Predicted Obinutuzumab Exposures at Steady-State (1000 mg Every 26 Weeks Doses) using the Integrated popPK Model

PK Parameter	Population	Statistic		
		Arithmetic Mean (SD)	Median (Range)	Geo. Mean (CV)
C_{max} µg/mL	Females (N=167)	483 (76.6)	478 (318-705)	478 (0.159)
	Male (N=29)	394 (65)	391 (292-547)	389 (0.166)
	Total (N=196)	470 (81.3)	468 (292-705)	463 (0.176)
AUC µg/mL*day	Females (N=167)	9,640 (4,080)	8,980 (3,720-39,500)	8,980 (0.382)
	Male (N=29)	8,160 (2,810)	7,630 (3,120-14,800)	7,680 (0.375)
	Total (N=196)	9,420 (3,950)	8,740 (3,120-39,500)	8,770 (0.385)

AUC = area under the concentration-time curve; C_{max} = maximum observed serum concentration; SD = standard deviation

In LN patients the steady state clearance of obinutuzumab was approximately 0.13 L/day with a median elimination $t_{1/2}$ of 22.4 days.

Figure 14 Conditional simulations: 5 doses

The covariate factors and patients' individual random effects were used to simulate concentration profiles following 1000 mg IV doses at 0, 14, 168, 182, and 364 days. Residual variability was not included. Median (**red**), and 5th and 95th percentiles (**blue**) of the simulated concentrations are plotted.

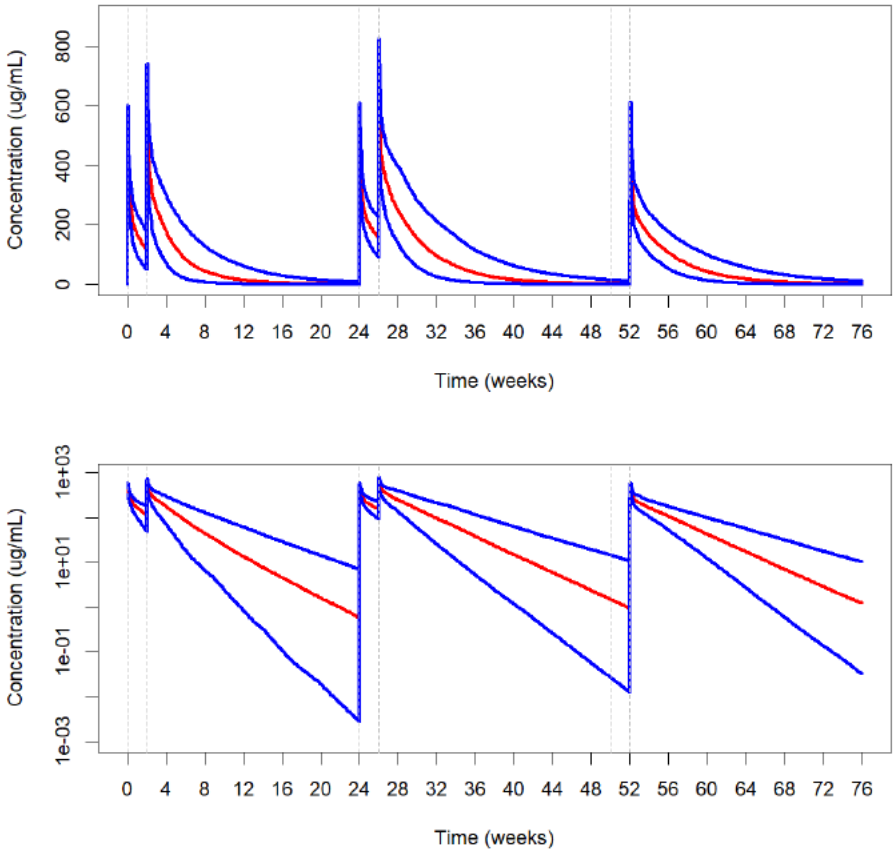
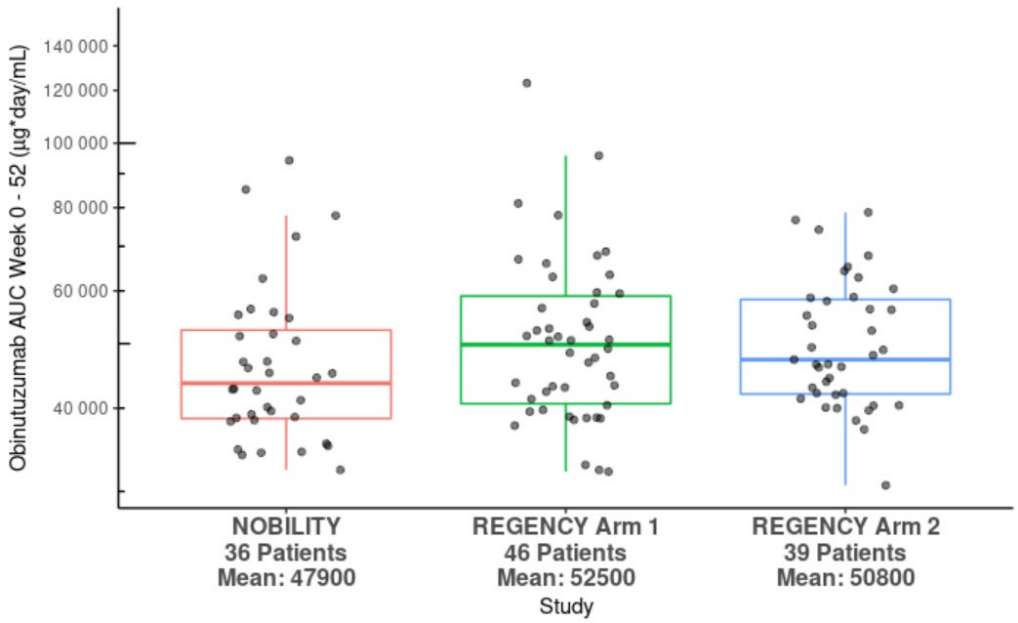


Figure 15 Comparison of NCA Derived Obinutuzumab Exposures (AUC_{0-52}) in the NOBILITY and REGENCY Studies



AUC = area under the concentration-time curve; NCA = Non-compartmental analysis
Note: Arm 1 (2-2-2 regimen), Arm 2 (2-2-1 regimen).

Special populations

Effects of intrinsic factors on the pharmacokinetics of obinutuzumab

The covariates found to influence obinutuzumab PK parameters were baseline values of body weight, gender, serum albumin. The covariates found to influence both steady state and time-dependent clearance were serum IgG, and UPCR. As is typical for monoclonal antibodies, obinutuzumab clearance and volume parameters increased with body size:

- Clearance and volume parameters were 14.4 to 29.0% higher for a 99.3 kg patient compared to a 75 kg patient, and 22.6 to 38.3% lower for a 44.0 kg patient, respectively, compared to a 75 kg patient.
- Steady-state clearance was 31.6% higher in patients with low baseline albumin concentrations of 20 g/L compared to patients with a baseline albumin concentration of 35 g/L, and 9.7% lower in patients with baseline albumin concentrations of 43.1 g/L.
- Steady state clearance was 21.7% higher in patients with baseline IgG levels of 23.1 g/L compared to patients with IgG concentrations of 10 g/L, and 27.1% lower in patients with baseline IgG levels of 2.6 g/L.
- Baseline UPCR also influenced time-dependent clearance, which was 31% higher in patients with a baseline UPCR of 9.47 g/g, and 42.5% lower with a baseline UPCR of 0.285 g/g compared to patients with UPCR levels of 3 g/g.

A summary of the effects of covariates on the integrated popPK model parameters is presented in Table 4. The following relationships between baseline covariates and PK parameters were found to be statistically significant:

- Patients with higher body weight have higher time-dependent clearance, time-independent clearance, central volumes, and peripheral volumes
- Males have higher central volumes than females
- Patients with lower serum albumin levels have higher time-dependent clearance and time-independent clearance
- Patients with higher UPCR have higher time-dependent clearance
- Patients with higher IgG have higher time-independent clearance

The effect of body weight is consistent with what is observed with monoclonal antibodies and is likely due to increased catabolism and larger fluid compartments associated with greater body mass. Relationships between body weight and exposure are presented in Figure 16. Furthermore, the NCA analysis of data from NOBILITY and REGENCY studies indicated a slightly higher exposure in the lower body weight range, however, overlapping exposures are observed across the body weight ranges in these studies (Table 4). In addition, due to the shallow exposure response relationship, no dose adjustments based on body weight is warranted in adult patients with lupus nephritis.

The gender effect on volume was previously reported for obinutuzumab in haematological malignancies and is likely complementary to the body weight effect on volume, which might not fully account for differences in fluid compartment volume. Both Cmax and AUC were lower in males, likely reflecting the combined effect of sex on central volume and body weight on all model parameters (Figure 18).

Table 4 Summary of Covariate Effects in the Integrated popPK model

Parameter	Covariate	Reference Value	Covariate Value [a]	Covariate Effect Value (95%CI) (%)
CL_T, CL_{INF}	Body weight	75 kg	44.0 kg	-31.5 (-39.8, -22)
			99.3 kg	22 (13.9, 30.6)
V_c,	Body weight	75 kg	44.0 kg	-22.6 (-27.9, -16.8)
			99.3 kg	14.4 (10.2, 18.8)
	Sex	Female	Male	14.8 (6.2, 23.4)
V_p	Body weight	75 kg	44.0 kg	-38.3 (-43.3, -32.9)
			99.3 kg	29 (23.3, 34.8)
CL_{T0}	Albumin	35 g/L	20 g/L	221.6 (152.4, 309.8)
			43.1 g/L	-35.2 (-40.8, -29.1)
	UPCR	3 g/g	0.285 g/g	-42.5 (-53.6, -28.7)
			9.47 g/g	31 (17.9, 45.5)
CL_{INF}	Albumin	35 g/L	20 g/L	31.6 (13.9, 52.1)
			43.1 g/L	-9.7 (-14.4, -4.7)
CL_{INF}	IgG level	10 g/L	2.6 g/L	-27.1 (-36.7, -16)
			23.1 g/L	21.7 (11.5, 32.9)

CI = confidence interval; CL_{INF} = time-independent clearance; CL_{T0} = time-dependent clearance; IgG = immunoglobulin G; V_1 = central volume, V_2 = peripheral volume

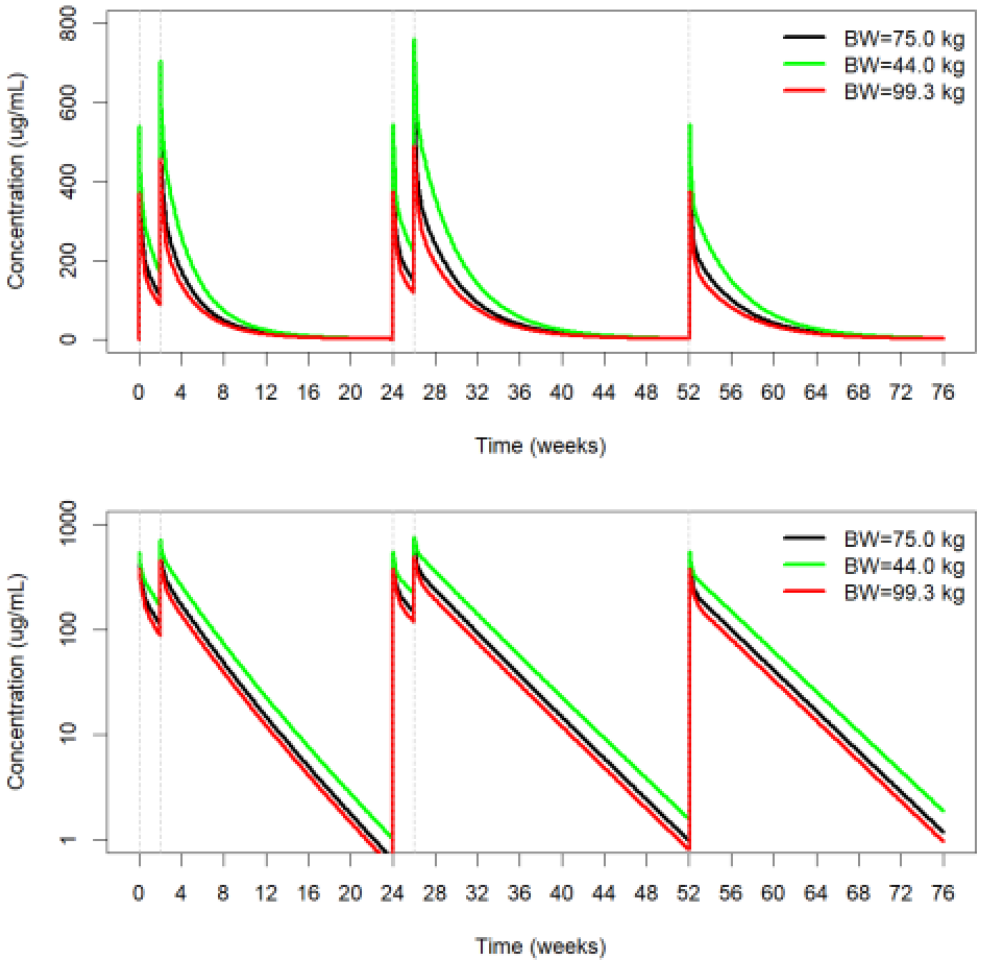
[a] Values represent the 2.5th and 97.5th percentiles of the values in the analysis data set.

The effects of serum albumin and UPCR likely reflect the impact of proteinuria on the elimination of obinutuzumab.

The effects of IgG likely reflect the impact of inflammation on the catabolism of obinutuzumab.

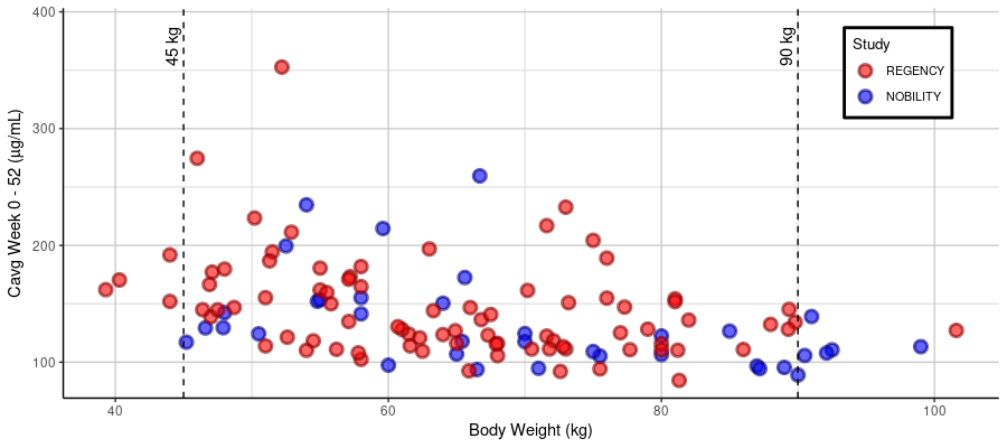
Additionally, disease specific covariates of FACIT-F, anti-dsDNA, serum complement C3, serum complement C4, eGFR, proteinuria, and serum creatinine were checked for their influence on PK parameters by diagnostic plots. None of these disease specific covariates had a clinically meaningful effect on obinutuzumab exposure up to Week 76.

Figure 16 Relationships between Body Weight and Exposure



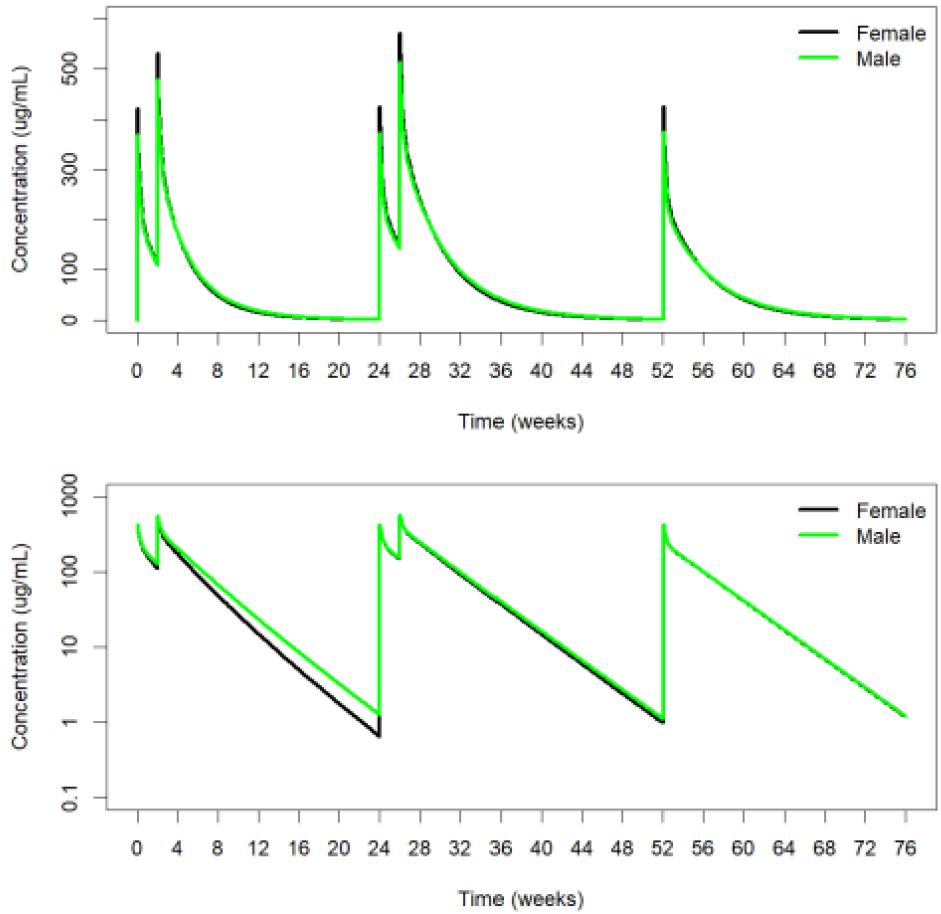
The covariate factors of a reference patient (albumin = 35 g/L, IgG = 10 g/L, UPCR = 3 g/g, female) and three values of body weight (44.0 kg, 75 kg, and 99.3 kg) were used to simulate concentration profiles following 1000 mg IV doses at 0, 14, 168, 182, and 364 days from the first dose.

Figure 17 Scatterplot of Obinutuzumab Exposure Parameter (C_{avg} Week 0-52) by Body Weight



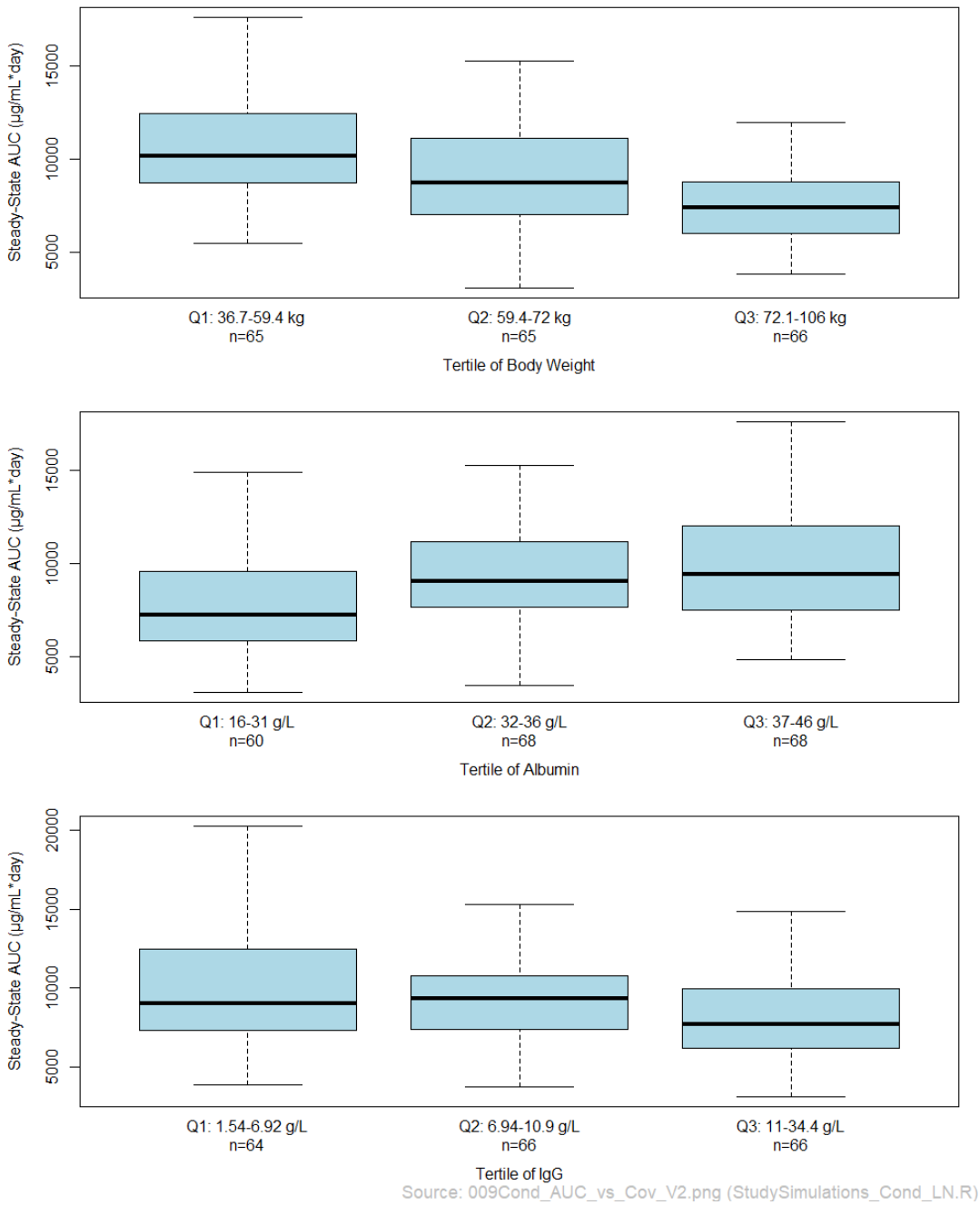
C_{avg} = average concentration

Figure 18 Relationships between Gender and Exposure



The covariate factors of a reference patient (weight = 75 kg, albumin = 35 g/L, IgG = 10 g/L, UPCR = 3 g/g) for female and male patients were used to simulate concentration profiles following 1000 mg IV doses at 0, 14, 168, 182 and 364 days after the first dose.

Figure 19 Box plots of Obinutuzumab Steady-State AUC (1000 mg every 6 months) By Baseline Tertiles of Body Weight (Top), Albumin (Middle), And IgG (Bottom)



Black line: median; box: interquartile range (IQR); whiskers: 1.5×IQR.

Pharmacokinetic interaction studies

Effects of extrinsic factors on the pharmacokinetics of obinutuzumab

No dedicated drug-drug interaction (DDI) studies were conducted. However, DDIs with drugs metabolized by the cytochrome P450 (CYP450) enzymes are not expected based on the clearance mechanism of obinutuzumab (Gazyvaro SmPC).

2.3.3. Pharmacodynamics

Mechanism of action

Obinutuzumab (also known as RO5072759, GA101, GAZYVARO) is a glycoengineered, recombinant, humanized, type II anti-CD20 mAb of the IgG1 subclass.

Compared to non-glycoengineered type 1 anti-CD20 antibodies, obinutuzumab has more direct B cell killing effects and reduced complement-dependent cytotoxicity (CDC) activity. Glycoengineering of the Fc portion of obinutuzumab, with reduced fucose content, promotes binding affinity for FcγRIII receptors on immune effector cells, such as natural killer (NK) cells and macrophages/monocytes, resulting in greater levels of ADCC and ADCP (Mössner et al. 2010; Herter et al. 2013; Reddy et al. 2017). As a result, obinutuzumab has potential to deplete CD20-positive B cells, including tissue-resident CD20-positive B cells to a greater degree than other anti-CD20 antibodies.

Lupus nephritis is the most common organ-threatening manifestation of SLE. Evidence suggests that B cells play a primary role in the pathogenesis of lupus nephritis, however randomized clinical trials with type 1 anti-CD20 antibodies rituximab and ocrelizumab failed to increase the rate of complete renal response (CRR) in patients with proliferative lupus nephritis (Rovin et al. 2012; Mysler et al. 2013). The lack of clinical response observed with type 1 anti-CD20 antibodies may be associated with incomplete depletion of pathogenic B cells in secondary lymphoid organs and tertiary lymphoid structures (Vital et al. 2011; Yusof et al. 2016; Yusof et al. 2017), supporting the hypothesis that greater B cell depletion would increase response rates. These data, combined with demonstrated greater B cell depleting activity, provided the mechanistic basis for the investigation of obinutuzumab as a potential therapy in lupus nephritis and other immunological diseases where the unmet medical need remains high and where type 1 anti-CD20 antibodies may be less effective due to incomplete depletion of pathogenic B cells in secondary lymphoid organs and tertiary lymphoid structures.

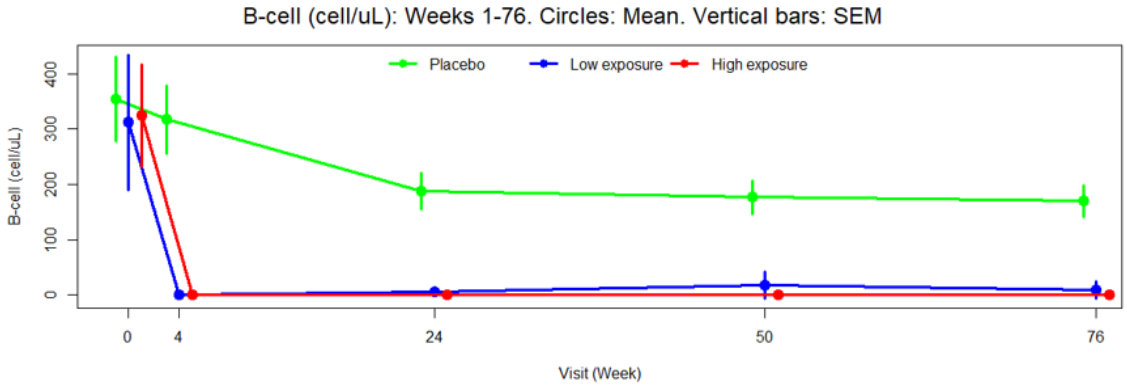
Primary and secondary pharmacology

For the purposes of exploratory analyses, patients were divided into two groups: a low exposure group (defined as AUC0-76 $<$ 37,671 μg/mL*day [median value]) or a high exposure group (defined AUC0-76 $\geq$ 36,749 μg/mL*day [median value]). B cell depletion was determined in both the NOBILITY and REGENCY studies using two assays: a conventional flow cytometry (TBNK) with a defined threshold of 10 cells/μL, and an additional high sensitivity flow cytometry (HSFC) assay, MRB1.1, with a lower limit of quantitation of 0.441 cells/μL of blood.

EXPOSURE-PHARMACODYNAMIC RELATIONSHIP

Peripheral CD19-positive B cell depletion was achieved following obinutuzumab treatment across the whole range of exposure in patients with lupus nephritis (Figure 20). Furthermore, exploratory graphical representations showed the sustained peripheral CD19-positive B cell depletion was maintained out to Week 184 for adequate responder patients (who continued in the blinded part of the study beyond Week 76 (Figure 21). However, the MAH noted that as of the clinical database lock, not all patients had reached Week 184 (n = 12 for the placebo group; n =11 for the low exposure group; n =7 for high exposure group), so the number of patients decreases over time but remains relatively high until Week 132 (n =42 for the placebo group; n = 21 for the low exposure group; n =26 for high exposure group). The shift after Week 76 to a single obinutuzumab dose every six months for all treated patients B cells continue to be depleted for both low and high exposure groups.

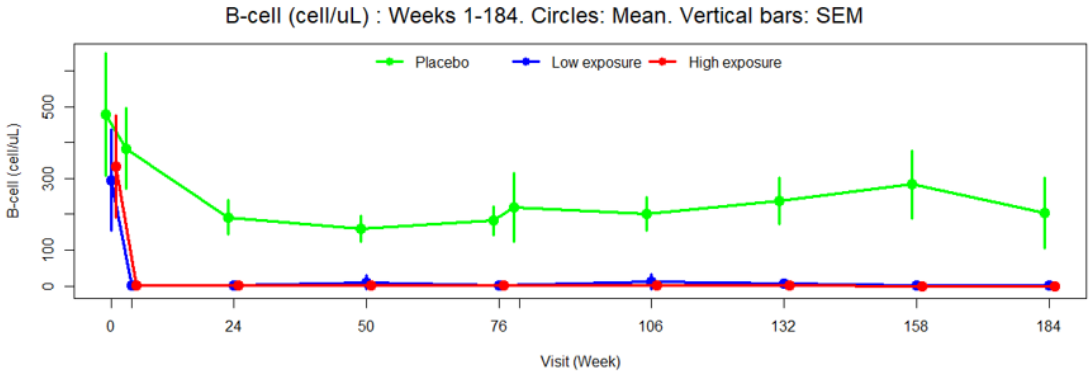
Figure 20 Mean (SEM) peripheral CD19-positive B cell Count time course (Weeks 1 to 76) (REGENCY Per protocol up to Week 76 Population and Placebo Population)



SEM = standard error of mean

Only patients in the REGENCY study from the per protocol plus placebo population who continued to the blinded period beyond week 76 were included.
Per-protocol up to Week 76 population plus placebo population was defined as patients on active treatment that received all doses at Weeks 0, 2, 24, and 26 and who also received 1 dose at Week 52 (2-2-1 regimen) or 2 doses at Weeks 50 and 52 (2-2-2 regimen), and all placebo patients (irrespective of the number of placebo doses received).

Figure 21 Mean (SEM) peripheral CD19-positive B cell Count time course (Weeks 1 to 184) (REGENCY Per Protocol up to Week 184 Population and Placebo Population)



SEM = standard error of mean
Only patients in the REGENCY study from the per protocol plus placebo population who continued to the blinded period beyond week 76 were included.
Per-protocol up to Week 184 population plus placebo population was defined as patients on active treatment that received all doses at Weeks 0, 2, 24, and 26 and who also received 1 dose at Week 52 (2-2-1 regimen) or 2 doses at Weeks 50 and 52 (2-2-2 regimen), and all placebo patients (irrespective of the number of placebo doses received).

In the Regency study, 99.2% (127 out of 128) of evaluable patients treated with obinutuzumab were B-cell depleted (defined as CD19+ B-cell counts < 10 cells/µl) at Week 4 and 95% (117 out of 123) were B cell depleted at Week 76.

Reductions in circulating naïve B, memory B, and plasmablasts/plasma cells were observed by Week 4 and remained low through Week 76 after treatment initiation.

IMMUNOGENICITY

Nobility study

A total of 64 patients were included in the safety analysis population, of whom 63 patients had available ADA samples. A total of 7 patients (7 out of 63 patients; 11.1%) from the obinutuzumab arm had at least 1 positive ADA titer at any time during the treatment period.

- In 5 of these patients (5 out of 63 patients; 7.9%) ADA titer became positive after initiation of obinutuzumab (treatment-induced ADA).
- Two patients had ADA-positive samples at baseline, one patient remained ADA-positive through Week 104 (treatment-unaffected; all titer values ≤baseline value), and in the second patient, all post-baseline samples were ADA-negative (treatment-unaffected).

The effect of obinutuzumab on levels of CD19-positive B cells was assessed over time through Week 104. ADA status had no effect on B cell depletion or exposure in the NOBILITY study. In the 5 patients with treatment-induced ADAs, peripheral CD19-positive B cells were profoundly reduced at the time points when positive ADA titers were recorded (Weeks 12, 24, 79, and BCFU month 6) compared to baseline values. Similarly, in the 1 patient who had ADA-positive samples through Week 76, CD19-positive B cells at baseline prior to obinutuzumab infusion were 67.4 cells/µL, and were below the lower limit of quantitation (BLQ) of a high sensitivity flow cytometry (HSFC) assay (BLQ: < 0.441 cells/µL of blood) at every timepoint tested up to and including Week 76 following obinutuzumab administration, except for a B cell value of 0.63 cells/µl at Week 24.

Overall, 40% (2 of 5 patients) of patients who had a treatment-induced ADA response in the NOBILITY study responded to treatment. However, the potential impact of ADA status on efficacy in the NOBILITY study is limited by the number of patients with an ADA response.

Regency study

A total of 136 patients were included in the safety analysis population, of whom 133 patients had available ADA samples. A total of 5 patients (5 out of 133 patients; 3.75%) from the obinutuzumab arm had at least one positive ADA titer at any time during the treatment period up to the primary endpoint at Week 76.

In 1 of these patients (1 out of 133 patients; 0.75%) ADA titer became positive after initiation of obinutuzumab (treatment-induced ADA). In 4 patients with ADA-positive samples at baseline, 1 remained ADA-positive through Week 76 (treatment-unaffected; all titer values ≤ baseline value). Two patients had all post-baseline samples that were ADA-negative, and the fourth patient had ADA-negative post-baseline samples except for an ADA-positive sample at Week 24 pre-infusion. This patient was also considered to be treatment-unaffected as the titer of the sample at Week 24 was less than 4-fold greater than the titer of the baseline sample (ADA titers of 1:10 at Baseline and <1:10 at Week 24). For the 1 patient with treatment-induced ADAs, positive ADA titers were recorded at pre-infusion Week 24 and Week 76.

ADA status had no clear effect on B-cell depletion in the REGENCY study. In the patient with treatment-induced ADAs, peripheral CD19-positive B cells were depleted BLQ of a HSFC assay (BLQ: <0.441 cells/µL of blood) at Weeks 24 and Week 76 when positive ADA titers were recorded. Similarly, in the patient who had ADA-positive samples through Week 76, CD19-positive B cells at baseline prior to obinutuzumab infusion were 207.8 cells/µL and were BLQ at every timepoint tested up to and including Week 76 following obinutuzumab administration.

The potential impact of ADA status on efficacy could not be assessed in the REGENCY study due to the limited number of patients with an ADA response.

Across both clinical studies, the overall incidence of treatment-emergent ADAs (e.g, patients were ADA-negative or had missing data at baseline, but developed an ADA response following study drug exposure, or were ADA-positive at baseline and the titer of one or more post-baseline samples was at least 4-fold greater than the titer of the baseline sample) ADAs was 3% (6 patients out of 200). There was no

evidence to suggest that the ADAs were neutralizing as the serum concentration-time profiles in ADA-positive patients were similar to those observed in ADA-negative patients. There was no loss of pharmacological activity (effects on B cells) in ADA-positive patients. None of the 12 patients with positive ADA titers at any time during the treatment period experienced an IRR or anaphylactic or hypersensitivity reaction during the study.

2.3.4. PK/PD modelling

Exposure-response analyses

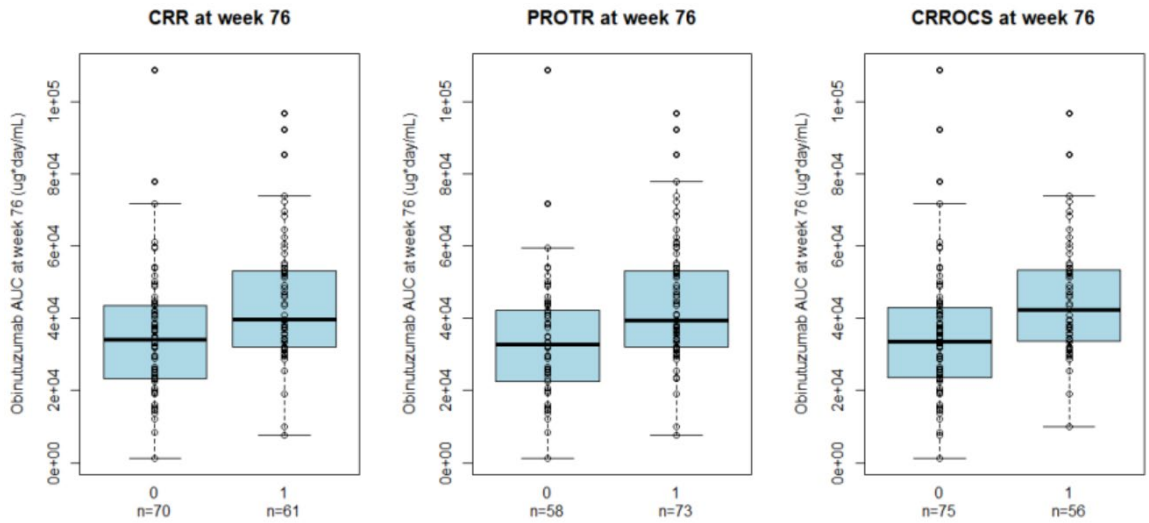
Data from REGENCY study were used for the exposure-efficacy and exposure-PD (biomarker) analyses, while the data from NOBILITY and REGENCY studies were used for the exposure-safety analyses. Individual predicted exposures (Cmax, AUC50, and AUC76) were computed for each patient using the final Pop PK model. For efficacy, AUC76 was the primary exposure metric. For Week 50 endpoints and exposure-safety analyses, AUC50 was used. Efficacy assessments and evaluation of adverse events were made at or up to Week 76. For infusion-related reactions or early SAEs, Cmax, following that dose at which it was observed, was used as an exposure measure.

ANALYSES OF EXPOSURE-EFFICACY RELATIONSHIP

Landmark analyses of exposure-response were performed at Week 76 for efficacy endpoints: complete renal response (CRR), proteinuric response, CRR with prednisone taper, death or renal-related events and at Week 50 overall renal response using the associated AUCs. Logistic regression models were implemented using individual covariate values and random effects. Confidence intervals were generated based on 1000 bootstrap samples drawn with replacement.

Both graphical and logistic regression analyses were conducted to investigate the relationship between cumulative PK exposure to obinutuzumab over 76 weeks (AUC0-76) and the probability of achieving CRR at Week 76. Individual predicted exposures (Cmax, AUC0-24, AUC0-50 and AUC0-76) were computed for each subject in the REGENCY study, and cumulative AUC0-76 was used as the primary measure of exposure to investigate exposure-efficacy relationships.

Figure 22 Distributions of Obinutuzumab Exposure for Responders and Non-responders (All Active Arm Patients)



CRR = complete renal response; CRROCS = CRR with successful prednisone taper; n = number of patients with evaluable data; PROTR=proteinuric response

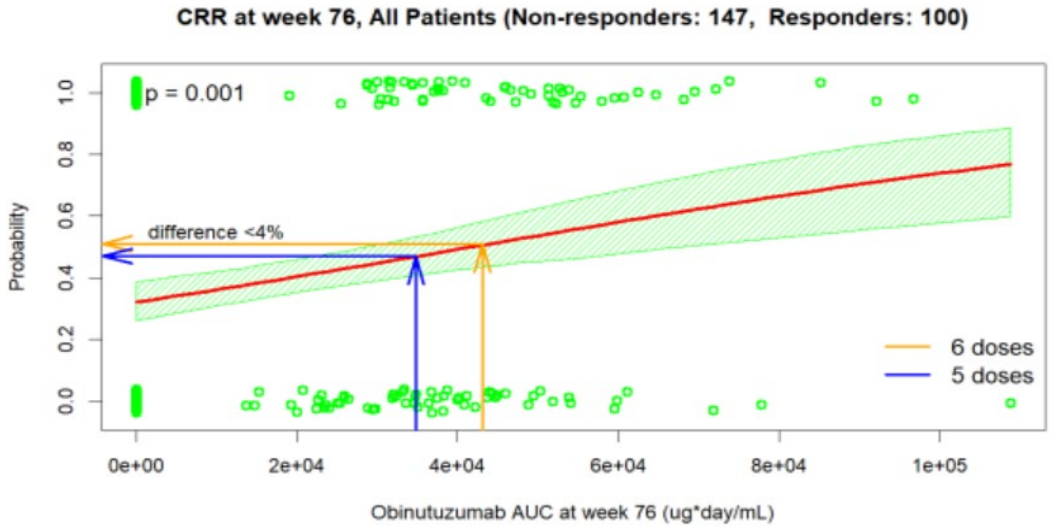
0 indicates non-responder; 1 indicates responder

The individual exposure values are plotted using a box and whisker plot. Median values are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles.

Table 5 Logistic regression models for renal response vs. exposure (per protocol patients)

Response type	Exposure metric	Patient group	Number		Intercept	Slope	p-value
			Patients	Responders			
CRR at week 76	AUC_{76}	All	247	100	-0.747	1.79e-05	0.001
		Active	115	55	-1.48	3.34e-05	0.009
	$Log(AUC_{76})$	Active	115	55	-17.6	1.66	0.003
PROTR at week 76	AUC_{76}	All	246	123	-0.367	1.9e-05	0.001
		Active	115	67	-1.1	3.51e-05	0.010
	$Log(AUC_{76})$	Active	115	67	-16.8	1.62	0.003
CRROCS at week 76	AUC_{76}	All	247	94	-0.833	1.69e-05	0.002
		Active	115	52	-1.39	2.85e-05	0.020
	$Log(AUC_{76})$	Active	115	52	-16.4	1.53	0.005
RDTH at week 76	AUC_{76}	All	248	66	-0.654	-2.15E-05	0.003
		Active	116	20	-1.05	-1.28E-05	0.424
	$Log(AUC_{76})$	Active	116	20	10.3	-1.12	0.086
ORR at week 50	AUC_{50}	All	228	123	-0.149	2.27e-05	0.009
		Active	112	67	-0.911	4.75e-05	0.022
	$Log(AUC_{50})$	Active	112	67	-13.6	1.38	0.014

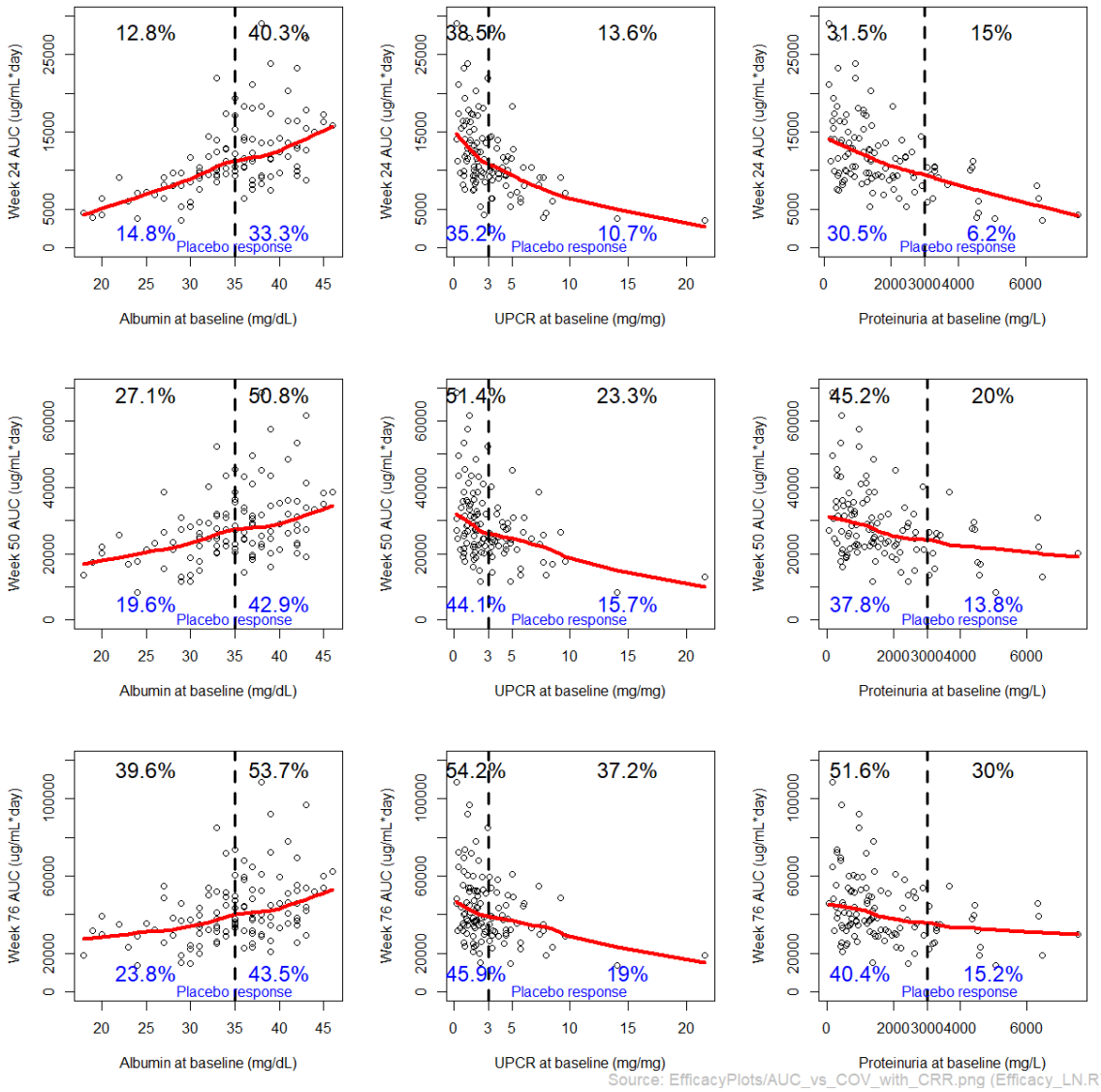
Figure 23 Logistic Regression for Probability of CRR at Week 76 vs. AUC_{0-76}



AUC = area under the concentration-time curve; CRR = Complete Renal Response.

Green circles illustrate the observed response (vertically jittered for better visualization). Red lines show the logistic regression lines. Shaded regions are the 90% confidence intervals for the regression line. The blue and orange arrows indicate the predicted probability of CRR for the simulated median of AUC_{0-76} corresponding to the 2-2-1 and 2-2-2 regimens of obinutuzumab, respectively.

Figure 24 Exposure and CRR response versus disease severity covariates related to lupus nephritis disease status at Week 24 (top row), Week 50 (middle row), and Week 76 (bottom row)



AUC = area under the concentration-time curve; UPCR = urine protein to creatinine ratio
Black circles represent the observed exposure (AUC). Red lines show regression lines. Black vertical dashed lines indicate covariate threshold values associated with disease severity (35 mg/dL for albumin, 3 mg/mg for UPCR and 3000 mg/L for proteinuria). Percentage numbers display CRR response rates in the placebo arm (blue) and the active arm (black) at Week 24 (top row), Week 50 (middle row), and Week 76 (bottom row) for patients with covariate values on either side of the threshold lines.

The REGENCY study was not powered to assess whether a dosing regimen with 5 or 6 doses up to Week 76 would result in a statistically significant difference in CRR. The logistic regression model, along with the pop-PK model, were used to conduct a clinical trial simulation aimed at determining whether a larger clinical trial would show a clinically significant increase in the percentage of CRR responders when 6 doses are given instead of 5.

The baseline covariates of the 196 patients in the Pop PK dataset and the random effects of the Pop PK model were sampled 100 times from their corresponding distributions to create a virtual population of 19,600 patients to describe the IIV. To account for the uncertainty in the logistic regression, 1000 logistic regressions were performed using 1000 bootstrap samples drawn with replacement from the logistic regression analysis population to generate a distribution of 1000 sets of intercept and slope parameters.

Each set was then used to predict a mean CRR value using the simulated AUC0-76 for each dosing regimen, and the difference in CRR between the 2-2-1 and 2-2-2 regimens was computed.

The simulations indicated that the median difference in the percentage of CRR responders between the two regimens was 3.8% (95% CI: 1.6% to 5.8%), suggesting no clinically significant difference between the regimens.

Table 6 Simulated and observed CRR response rate by Obinutuzumab dosing arm per protocol population

Regency Dosing Regimen (Number of patients)	Observed CRR response rate (%) (95% CI)	Predicted CRR Response Rate and 95% CI (%)		
		Point Estimate (%)	Bootstrap median (%) (95% CI)	Median difference in response rate: (%) (95% CI)
2-2-1 (N=59)	47.5 (34.7-60.2)	47.9	47.9 (40.3-55.6)	3.8 (1.6-5.8)
2-2-2 (N=56)	48.2 (35.1-61.3)	51.7	51.7 (42.8-60.7)	

CI = confidence interval; CRR = Complete Renal Response

Per-protocol up to Week 76 population was defined as patients on active treatment that received all doses at Weeks 0, 2, 24, and 26 and who also received 1 dose at Week 52 (2-2-1 regimen) or 2 doses at Weeks 50 and 52 (2-2-2 regimen) doses. There were two patients who were assigned to receive the 2-2-2 regimen but missed the dose at Week 52. They were included in the 2-2-1 regimen group.

ANALYSES OF EXPOSURE-SAFETY RELATIONSHIP

The following classes of AEs were considered:

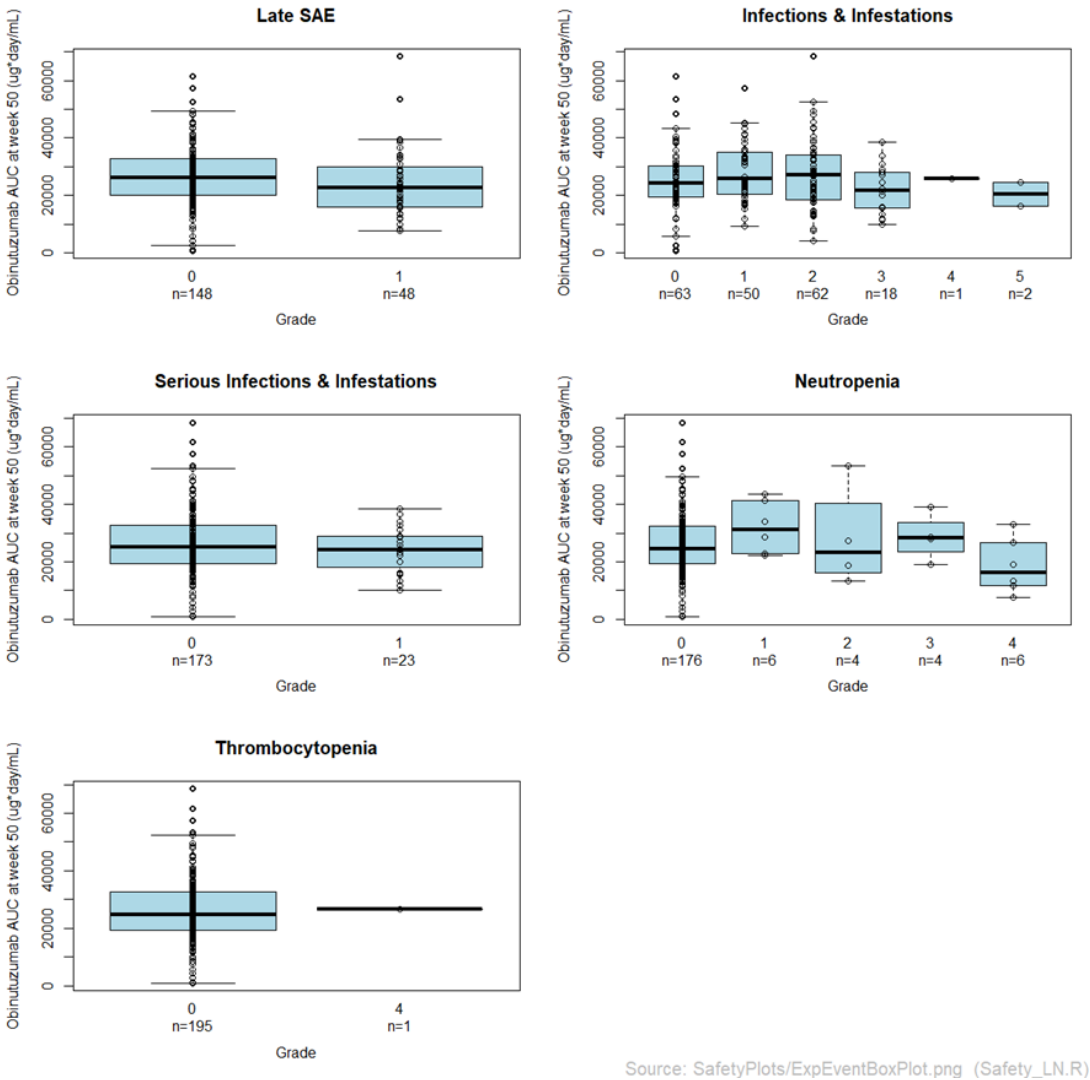
- Early SAEs, i.e. occurring between the first and the second dose of obinutuzumab
- Infusion-related reactions (IRR) after each dose i.e., dose 1 (IIR_1), dose 2 (IIR_2), dose 3 (IIR_3), etc.
- Late SAEs, i.e. excluding early SAEs and IRRs
- AEs of infection and infestation
- AEs of neutropenia
- AEs of thrombocytopenia

For each of the AEs considered, the following analyses were performed:

- Distributions of exposures for patients with and without events were compared.
- Individual observed obinutuzumab concentration profiles were overlaid; the profiles of patients with at least one event were highlighted and compared with the profiles of patients without the events.

Logistic regression models were implemented to assess the correlation between the probability of occurrence of a specific AE and exposure (Table 7). The logistic regression analyses showed no significant positive correlations between the exposure and the probability of AEs, except for neutropenia. A significant relationship (p=0.015) was found between exposure and the occurrence of any grade of neutropenia. However, for neutropenia AEs of Grade 3 and above, the relationship approached but did not reach statistical significance (p=0.056). In both cases, the relationships are weak and may not be considered clinically relevant (Figure 26).

Figure 25 Obinutuzumab Exposure (AUC_{0-50}) for Patients with and without Main Adverse Events: All Active Arm Patients



Source: SafetyPlots/ExpEventBoxPlot.png (Safety_LN.R)

AUC_{0-50}= area under the concentration-time curve from time 0 to 50 hours post-dose; n = number of patients with evaluable data

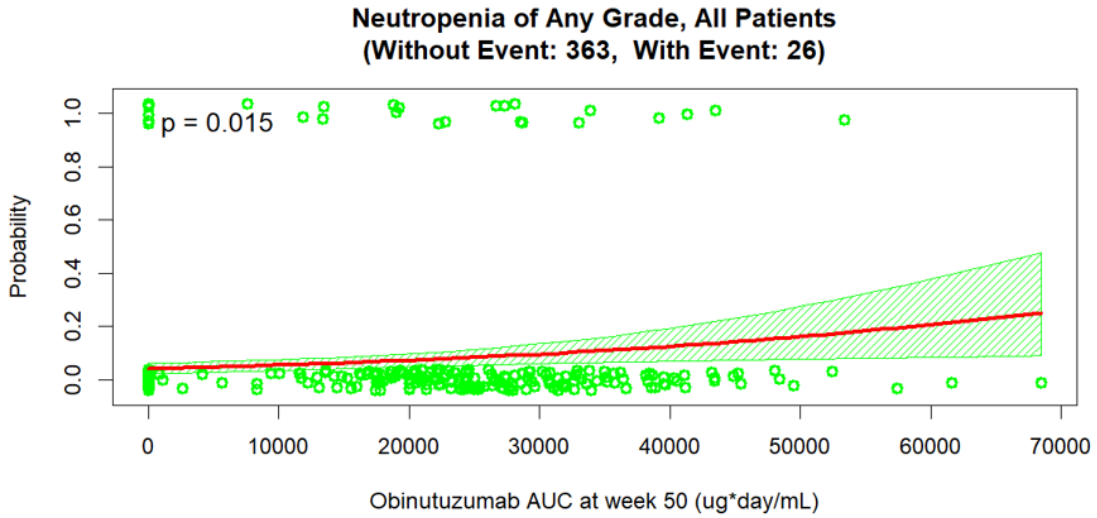
Median values are designated by black lines in the center of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles.

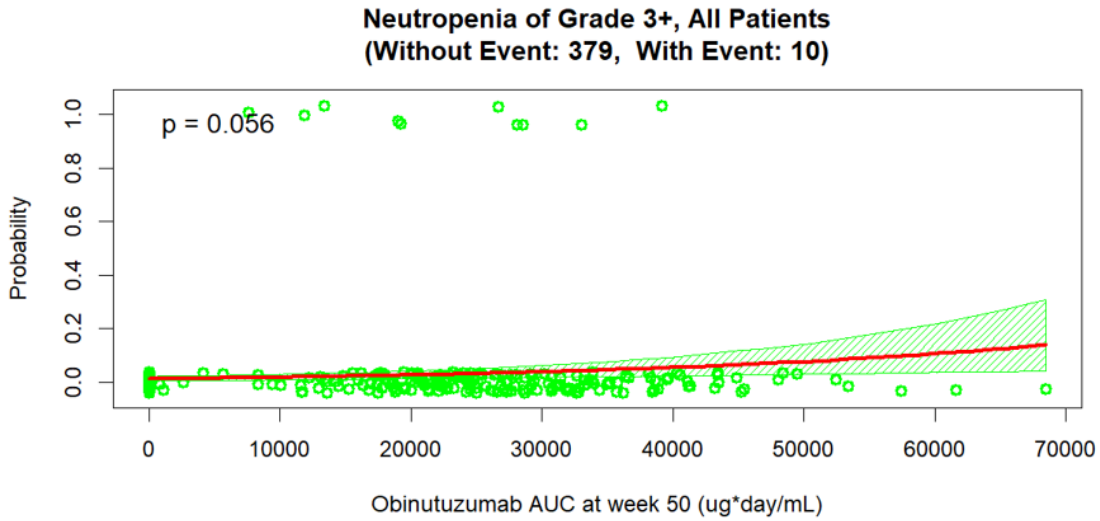
Table 7 Logistic regression models for adverse events vs. exposure (all patients)

Statistically significant increase of AE probability with exposure is shown in red font.

AE type	Grade	Patient group	Number of patients	Number of events	Intercept	Slope	p-value
Late SAE	Any	All	389	83	-1.36	4.19e-06	0.601
		Active	196	48	-0.51	-2.41E-05	0.137
Infections & Infestations	Any	All	389	249	0.413	1.27e-05	0.076
		Active	196	133	0.44	1.18e-05	0.411
	3+	All	389	39	-2.11	-6.76E-06	0.555
		Active	196	21	-1.02	-4.53E-05	0.060
Serious Infections & Infestations	Any	All	389	41	-2.15	5.52e-07	0.959
		Active	196	23	-1.38	-2.53E-05	0.248
Neutropenia	Any	All	389	26	-3.13	2.98e-05	0.015
		Active	196	20	-2.25	2.91e-06	0.892
	3+	All	389	10	-4.27	3.59e-05	0.056
		Active	196	10	-2.05	-3.58E-05	0.277
Early SAE	Any	All	389	10	-3.44	-0.00093	0.504
		Active	196	5	-0.25	-0.00804	0.020
IRR after Dose 1	Any	All	389	33	-2.42	0.000192	0.801
		Active	196	21	2.69	-0.0112	0.001
	3+	All	389	3	-4.61	-0.00126	0.627
		Active	196	2	0.0851	-0.0121	0.006
IRR after Dose 2	Any	All	389	12	-3.3	-0.00052	0.607
		Active	196	6	1.54	-0.00931	0.042
	3+	All	389	1	-6.27	0.000946	0.779
		Active	196	1	5.95	-0.0237	0.064

Figure 26 Logistic Regression for Probability of Neutropenia vs. Exposure





Green circles illustrate the observed response (vertically jittered for better visualization).
Red lines show the logistic regression lines.
Shaded regions are the 90% confidence intervals for the regression line.

2.3.5. Discussion on clinical pharmacology

Pop PK modelling

Data came from study WA29748 (Nobility) and study CA41705 (Regency) and included 3326 sample results from 196 patients with LN. A new Pop PK model was developed with a 2-compartment structure for obinutuzumab LN, with a split time independent and time-dependent decay clearance parameter in the central compartment. In the time dependent clearance, total clearance (CL) is the sum of two elimination pathways, (i) a time-dependent clearance that decreases over time exponentially with a decay coefficient (k_{des}), likely related to CD20 target reduction and proteinuria improvement over time and (ii) a time-independent clearance related to the endogenous catabolic processes of IgG. Effect of body weight was incorporated by allometric scaling with estimated exponents. Other covariate effects included in the final model were baseline albumin concentration (influencing both steady state and time-dependent clearance), baseline IgG, baseline UPCR, and sex

Pharmacokinetics in the target population using NCA

In the Nobility Phase 2 study, one dosing regimen was used, namely obinutuzumab 1000 mg administered as an absolute (flat) dose by IV infusion on Days 1, 15, 168 (week 24), and 182 (week 26) or placebo. Sampling for PK was collected at Day 1 pre-dose, Day 1 post-dose, week 2 pre-dose, week 2 post-dose, Weeks 4, 12, week 24 pre-dose, week 24 post-dose, week 26 pre-dose, week 26 post-dose and week 36 and week 52 or at early termination visit. This was considered sufficient for estimating exposure and variability of exposure in patients. The CHMP noted that several patients were BLQ (0.004 mg/L) already at pre-dose (C_{trough}) on Week 24, but only one out of these 5 patients showed breakthrough of B cells just prior to the next dosing cycle. Moreover, this patient showed continued decrease in anti-dsDNA during the course of the clinical study with the lowest level in week 52. Hence, decrease of obinutuzumab serum levels to BLQ intermittently did not preclude pharmacodynamic effect. Since the pathologic IgG in LN most likely has a half-life of 18-21 days, the effect of obinutuzumab in LN is delayed compared to the fast depletion of B-cells.

At week 12, the variation in serum concentration was already very large (0.048 to 64.7 mg/L). However, the levels of CD19-positive B cells in the obinutuzumab + MMF arm patients remained profoundly reduced through Week 12 (BLQ in >90% of the patients).

C_{max}, C_{trough} and AUC_{0-24} and AUC_{24-52} was reported for 42-48 patients. The variability (CV) on C_{max} and AUCs was moderate (28.2-58.0), whereas variability on C_{trough} was high (355-472). This finding was expected considering the long-time interval between dosing cycles and was found acceptable as reestablishment of B cell population is slow.

C_{max} was similar at Day 1 and week 24. However, AUC increased from cycle 1 (15300 µg/mL*days) to cycle 2 (29800 µg/mL*days). This was expected to some extent, since in the majority of patients, obinutuzumab was still present in serum at the time of cycle 2 dosing and clearance is decreasing over time. Dose proportionality was not investigated in LN patients. This was agreed by the CHMP.

The Regency study was evaluating if a dosing regimen of 2-2-1 every 6 months (Day 1, week 2, week 24, week 26 and week 52) was sufficient to provide efficacy as opposed to a 2-2-2 regimen (Day 1, week 2, week 24, week 26, week 50 and week 52). In the Nobility study, only a 2-2 dosing regimen (Day 1, week 2, week 24 and week 26) was used. Hence, a single maintenance dose every 6 months is tested as opposed to a double maintenance dose. The proposed 2-2-1 regimen correlates with the finding of clearance decreasing over time due to normalization of kidney function, decreased inflammation and precipitation of B-cell population carrying the target. The CHMP noted that less frequent maintenance doses are also used for the other indications CLL and FL, although with higher frequency of 1 and 2 months, respectively, than for the LN indication of every 6 months.

Obinutuzumab serum concentration data up to Week 76 were analyzed in the PK-evaluable patient population, i.e. patients with full PK sample collection. The analysis was conducted providing exposure estimates (C_{max}, AUC, and C_{trough}) for Weeks 0 to 24, Weeks 24 to 52, Weeks 52 to 76, and an estimate of cumulative exposure up to Week 76 for the two dosing regimens (2-2-1 and 2-2-2).

As expected, the cumulative exposure was higher for the 2-2-2 regimen with Geometric mean AUC_{0-76d} of 85500 µg/mL*days (CV 26.7%) than for the 2-2-1 regimen where geometric mean AUC_{0-76d} was 72900 µg/mL*days (CV% 20.6). This 15% higher exposure, corresponds closely to the 17% higher dose.

When using the POPPK model to estimate this accumulated exposure, a difference was observed between the NCA derived AUC_{0-76d} (arithmetic mean 88600 µg/mL*day) and the predicted AUC_{0-76d} (arithmetic mean 36800 µg/mL*day). The model estimated exposure aligned closer with AUC of 5 doses of 1000 mg (when one dose equals a model estimated AUC of 8700 ug/mL*days at steady state) than the NCA estimate. It could be that, for NCA the PK sampling is missing out on the distribution phase, anticipating a 1-compartmental decline in concentration over time. Moreover, more data points are included in the

model estimate from patients with incomplete sampling and patients from the NOBILITY study. Hence, this may explain the higher AUC using NCA.

Section 5.2 of the SmPC is updated to include the pharmacokinetics properties of obinutuzumab in LN patients derived from the simulations.

Overall, the incidence of ADA was very low across Nobility and Regency studies. In the event ADA was present, no impact on exposure was observed.

Special Populations

The impact of intrinsic factors on primary PK parameters clearance and volume was investigated using the integrated POPPK model. The factor with the highest impact was baseline serum albumin, which is a factor that is expected to change over time as the patient's renal function improves during the course of the treatment with obinutuzumab. Serum albumin of 20 g/L was estimated to increase CL at baseline (CL_{T0}) with up to 300% compared to the reference value of 35 g/L, whereas CL at steady state would increase with up to 50% (CL_{inf}). The impact of other factors such as body weight, sex, UPCR and IgG level was comparable to the interindividual variability on AUC of approximately 50% and therefore considered of limited clinical relevance. Moreover, as the dosing regimen of obinutuzumab in LN patients is less frequent than in the two other approved indications (CLL and FL) providing overall lower exposure, the impact of intrinsic factors is not a safety concern. The factor with the highest impact would be low serum albumin levels. However, this was not found as a concern for lack of effect since albumin levels are expected to rise in LN patients following obinutuzumab treatment and considering also the posology of obinutuzumab which is dosed twice within the first two weeks, hence, precipitation of B cells happens very quickly no matter the baseline clearance value.

Pharmacodynamics

Data from Regency study were used for the exposure-efficacy and exposure-PD (biomarker) analyses, while the data from Nobility and Regency studies were used for the exposure-safety analyses. The final Pop PK model was used to predict exposure metrics. The exposure-response relations were explored graphically and evaluated by logistic regression analyses.

Primary pharmacology

Depletion of CD19-positive B-cells was endorsed as a marker for anti-CD20 activity and previously used for approval of the haemato-oncological indications of Gazyvaro. Following obinutuzumab infusions at Week 0, 2, 24, 26, (50 for some patients) and 52 in the Regency study, the mean peripheral CD19-positive B-cell count decreased substantially towards 0, both in patients with obinutuzumab exposure higher and lower than median $AUC_{Week\ 76}$. The effect was evident from Week 4 and sustained throughout Week 76. In comparison, no change was seen for the placebo group. An extended analysis of mean peripheral CD19-positive B-cell count with treatment beyond Week 76 up to Week 184 showed sustained depletion for the obinutuzumab arms, while maintaining a constant baseline level for the placebo group. It was acknowledged that the sample sizes at several of the later time points are very small. These data supported depleting effects of obinutuzumab on CD19-positive B-cell at least up to Week 76 and presumably also after with repeated dosing. The pharmacodynamic response to obinutuzumab was consistent with the mechanism of action of obinutuzumab.

Very few patients developed ADAs post-baseline (NOBILITY: 5 patients, REGENCY: 1 patient). No effect of ADAs was seen on PD (CD19-positive B-cell depletion) or efficacy. Hence, immunogenicity was not considered a concern.

Exposure-efficacy:

Analyses of exposure vs clinical outcomes were provided. Logistic regression analyses showed a statistically significant positive relationship between CRR at Week 76 and AUC0-76, indicating higher probability for obtaining CRR at Week 76 with increased concentration of obinutuzumab. This exposure-response relationship was also evident for the key secondary endpoints of CRR with successful tapering and proteinuric response. The MAH argued that this finding is likely biased by baseline covariates relating to the severity of LN disease. A graphical illustration of exposure (reflected by AUC0-76) vs baseline albumin, UPCR and proteinuria at Week 24, 50 and 76, superposed with response rates in the obinutuzumab and placebo group showed that the exposure of obinutuzumab appears higher in patients with high baseline albumin and low baseline UPCR and proteinuria, which aligns with the finding that patients with low albumin exhibit higher clearance. The CHMP considered the seemingly positive exposure-efficacy relationship sufficiently justified.

Dosing regimen:

No actual dose-response relationships have been investigated, as only one dose (1000 mg i.v.) was provided in both the Nobility and Regency studies (see also discussion on clinical efficacy in Section 2.4.2.).

Logistic regression analysis of data from the Regency study at Week 76 based on AUC0-76 indicated that a dosing regimen with 5 doses instead of 6 up to Week 76 would not have clinically relevant influence on the probability of CRR (difference of about 4%). These results, also supported by clinical trial simulations, indicated that the clinical response when receiving only one dose obinutuzumab at Week 52, was expected to be similar to the response when receiving a dose at both week 50 and 52. However, the CHMP acknowledged that the chronic dosing of one dose of 1000 mg obinutuzumab every 6 months is based on the very limited sample size in the blinded obinutuzumab arm beyond Week 76 in the Regency study.

Exposure-safety:

Exposure-safety analyses were performed on the pooled data from both the Regency and Nobility studies, and logistic regression models used to assess the correlation between probability of specific AEs and exposure. These simulations detected a significant positive relationship between exposure and neutropenia AEs (any grade) of p=0.015, while a tendency towards a positive relationship with neutropenia AEs of ≥Grade 3 (p=0.056). Neutropenia is an adverse drug reaction with a frequency very common in the SmPC Section 4.8 and Grade 3-5 neutropenia is an adverse reaction with a frequency common. Otherwise, no exposure-safety relationships were found.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of obinutuzumab was sufficiently characterised in lupus nephritis patients.

Obinutuzumab appears to have sufficient CD19-positive B-cell depleting effects at least up to Week 76 and the pharmacodynamic response to obinutuzumab was consistent with the mechanism of action of obinutuzumab.

2.4. Clinical efficacy

The efficacy results supporting this application are derived primarily from the pivotal Phase III Study CA41705 (referred to as "REGENCY", ongoing at time of submission) and the supportive Phase II Study WA29748 (referred to as "NOBILITY", completed). Both studies are global, prospective, double-blind, randomised, placebo-controlled, parallel-group, multicenter studies in patients with International Society

of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Class III or IV lupus nephritis with or without concomitant Class V disease.

Table 8 Summary of studies contributing to efficacy evaluation

Protocol Name/Number	Population	Study Design	Criteria for Evaluation	Dose, Route, and Regimen	Number of Patients	Study Status
Pivotal Study						
REGENCY (CA41705)	Patients with ISN/RPS 2003 Class III or IV with or without concomitant Class V lupus nephritis treated with SoC therapy with MMF and corticosteroids [a]	Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Efficacy, safety, pharmaco-kinetics, pharmaco-dynamics, and immuno-genicity	**Blinded Treatment (up to Week 76 Visit [Primary Endpoint Assessment])** **Obinutuzumab Arm** Obinutuzumab Arm 1 (2-2-2 Regimen): Obinutuzumab 1000 mg IV on Day 1 and Weeks 2, 24, 26, 50, and 52 (corresponding to Days 1, 14, 168, 182, 350, and 364, respectively) [b] Obinutuzumab Arm 2 (2-2-1 Regimen): Obinutuzumab 1000 mg IV on Day 1 and Weeks 2, 24, 26, and 52 (corresponding to Days 1, 14, 168, 182, and 364, respectively) [b] To preserve the blind, patients received placebo infusion at Week 50 **Placebo Arm** Placebo infusion on Day 1 and Weeks 2, 24, 26, 50, and 52 (corresponding to Days 1, 14, 168, 182, 350, and 364, respectively) [b] **Beyond Week 76 Visit** • Patients with an adequate response at Week 76 continued their blinded infusion at Week 80 and every 6 months thereafter until study unblinding. • Patients with an inadequate response at Week 76 were eligible for OLT. OLT follows the initial obinutuzumab treatment schedule with infusion on OLT Day 1 and at OLT Weeks 2, 24, 26, 52, and every 6 months thereafter. • All patients entered SFU for at least 12 months from the last dose of obinutuzumab or placebo, with the first SFU visit occurring approximately 6 months after the previous study visit (e.g., 6 months after Week 76).	**Efficacy-Evaluable** [c] Obinutuzumab Arm=135 (2-2-2 Regimen=69; 2-2-1 Regimen=66) Placebo Arm=136 **Post Week 76 Blinded Treatment Efficacy-Evaluable** [d] Obinutuzumab Arm=71 Placebo Arm=58	Ongoing (recruitment completed) Primary analysis CCOD: 15 August 2024
Supporting Study						
NOBILITY (WA29748)	Patients with ISN/RPS 2003 Class III or IV with or without concomitant Class V lupus nephritis treated with SoC therapy with MMF/MPA and corticosteroids [e]	Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Efficacy, safety, pharmaco-kinetics, pharmaco-dynamics, and immuno-genicity	**Blinded Treatment (up to Week 52 Visit [Primary Endpoint Assessment)** **Obinutuzumab Arm** Obinutuzumab 1000 mg IV on Day 1 and Weeks 2, 24, and 26 (corresponding to Days 1, 15, 168, and 182) [f] **Placebo Arm** Placebo infusion on Day 1 and Weeks 2, 24, and 26 (corresponding to Days 1, 15, 168, and 182) [f] **Beyond Week 52 Visit** Patients continued to receive SoC treatment with follow-up visits at Weeks 76 and 104. No doses of obinutuzumab or placebo were administered after Week 26.	**mITT** [g] Obinutuzumab =63 Placebo=62 **Efficacy-Evaluable** [c] Obinutuzumab =64 Placebo=62	Completed Last Patient Last Visit (Final Analysis): 2 August 2023

ACE=angiotensin-converting enzyme; ARB=angiotensin-receptor blocker; CCOD=clinical cutoff date; CSR=clinical study report; ISN=International Society of Nephrology; IV=intravenous; mITT=modified intent-to-treat; MMF=mycophenolate mofetil; MPA=mycophenolic acid; OLT=open-label treatment; RPS=Renal Pathology Society; SCE=Summary of Clinical Efficacy; SFU=study follow-up; SoC=standard-of-care.

[a] SoC therapy included ACE inhibitor or an ARB for at least 10 days prior to randomization, MMF titrated by Week 4 to 2.0–2.5 g/day in divided doses, methylprednisolone 250–1000 mg IV (prior to or during screening or on Day 1 prior to first infusion of study treatment), and oral prednisone initiated at 0.5 mg/kg (maximum 60 mg/day) until Day 15 and tapered to a total daily maintenance dose of 5 mg/day by Week 24 (and maintained at this dose until Week 80). Details are provided in Table 4.

[b] Approximate Study Day numbers (timepoints were specified as Study Week in the REGENCY protocol); infusion visits except for Day 1 had to be performed within ±3 days of the scheduled visit as per protocol.

[c] The efficacy-evaluable population consisted of all randomized patients regardless of whether they received study treatment (obinutuzumab or placebo) (see Section 1.4.1). This analysis population was used to perform efficacy analyses up to Week 76 for REGENCY, and for post-hoc re-analysis of NOBILITY data presented in this SCE for supportive purposes.

[d] The Post Week 76 Blinded Treatment Efficacy-Evaluable population consisted of patients who were assessed as adequate responders and continued blinded treatment post Week 76 and reached the specified endpoint assessment visit by the CCOD (see Section 1.4.1). This analysis population was used to analyze post-Week 76 efficacy data for REGENCY.

[e] SoC therapy included either an ACE inhibitor or ARB at least 10 days prior to randomization, continuation or initiation of either MMF (2.0–2.5 g/day) or MPA (1440–1800 mg/day) during screening or no later than Day 1, methylprednisolone 1000 mg IV (prior to or during screening) and permitted up to a total of 3000 mg methylprednisolone IV prior to randomization, and oral prednisone initiated at 0.5 mg/kg (maximum 60 mg/day) and tapered over 10 weeks to a daily oral maintenance dose of 7.5 mg/day by Week 12 (and maintained at this dose until Week 52). Details are provided in Table 4.

[f] Approximate Study Week numbers (timepoints were specified as Study Day in the NOBILITY protocol); infusion visits except for Day 1 had to be performed within±3 days of the scheduled visit as per protocol.

[g] The mITT population consisted of all randomized patients who received any part of an infusion of study treatment (obinutuzumab or placebo) (see Section 1.4.1). This analysis population was used to perform efficacy analyses per study protocol and presented in the NOBILITY final CSR.

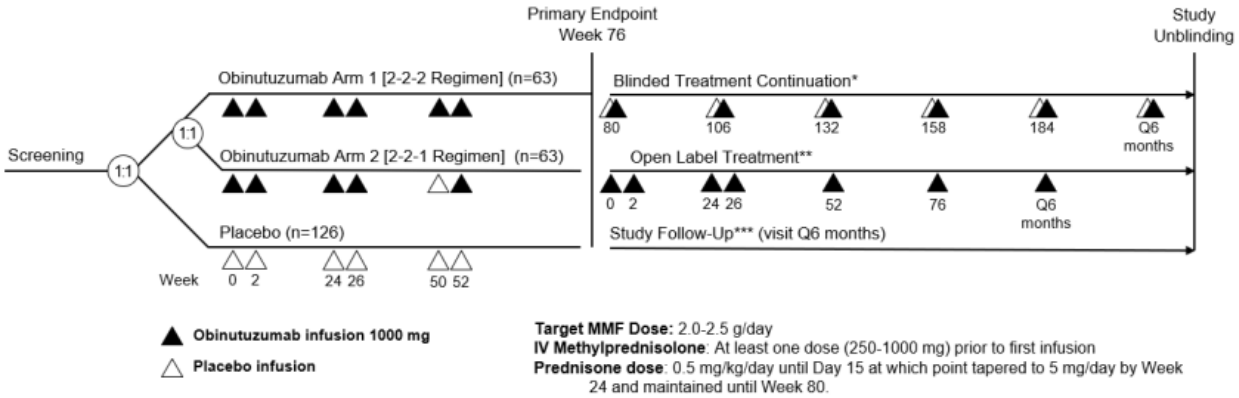
2.4.1. Main study

REGENCY (CA41705)

Methods

REGENCY is an ongoing pivotal Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study comparing the efficacy and safety of obinutuzumab versus placebo in patients with ISN/RPS 2003 Class III or IV with or without concomitant Class V lupus nephritis treated with SoC therapy with MMF and corticosteroids. The study has completed enrollment, with 271 patients enrolled from 10 August 2020 to 2 March 2023 completed.

Figure 27 CA41705 (REGENCY) Study schema



MMF = mycophenolate mofetil.
Note: The sample sizes shown are the planned patient recruitment numbers.
* 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.
*** Patients are followed through Week 76 and for at least 12 months from the last dose of obinutuzumab or placebo.

Study participants

Table 9 Key eligibility criteria for Regency and Nobility

REGENCY	NOBILITY
Key Inclusion Criteria	
Age 18–75 years	
Lupus nephritis diagnosis	

REGENCY	NOBILITY
Active or active/chronic ISN/RPS 2003 Class III or IV proliferative lupus nephritis by renal biopsy performed in the 6 months prior to screening or during screening One or more active glomerular lesions must be present. Class V disease may be present in addition to Class III or IV. The local biopsy report was used to determine eligibility.	Diagnosis of ISN/RPS 2003 Class III or IV lupus nephritis as evidenced by renal biopsy performed within 6 months prior to or during screening. Patients may co-exhibit Class V disease in addition to either Class III or Class IV disease. The local biopsy report was used to determine eligibility.
<u>Systemic lupus erythematosus (SLE) diagnosis</u>	
SLE according to the 2019 EULAR/ACR Classification Criteria, which are met by the presence of Class III or IV lupus nephritis (above) and current or past positive ANA (Aringer et al. 2019) Positive ANA is defined by ANA at a titer of $\geq$1:80 on HEp-2 cells or an equivalent positive ANA test at least once.	Diagnosis of SLE, according to the 2012 ACR criteria, whereby at least 4 criteria must be present, 1 of which must be a positive ANA (Hahn et al. 2012)
<u>Proteinuria</u>	
UPCR $\geq$1 g/g on a 24-hour urine collection at screening	Proteinuria (UPCR $>$1.0) based on a 24-hour urine collection
Key Exclusion Criteria	
Pregnant or breastfeeding/lactation	
<u>Severe renal impairment</u>	
Severe renal impairment, as defined by eGFR $<$30 mL/min/1.73 m^2 (as estimated using the CKD-EPI equation) or the need for dialysis or renal transplantation	Severe renal impairment as defined by eGFR $<$30 mL/minute or the need for dialysis or renal transplantation
<u>Rapidly progressive glomerulonephritis</u>	
Presence of rapidly progressive glomerulonephritis, defined by any of the following: crescent formation in $\geq$50% of glomeruli assessed on renal biopsy, sustained doubling of serum creatinine during the 2 months prior to screening, or the investigator's opinion that the patient has rapidly progressive glomerulonephritis	Presence of rapidly progressive glomerulonephritis, defined by the presence of crescent formation in $\geq$50% of glomeruli assessed on renal biopsy or sustained doubling of serum creatinine within 12 weeks of screening or investigator's opinion that the patient has rapidly progressive glomerulonephritis
<u>Infections</u>	

REGENCY	NOBILITY
Active infection of any kind, excluding fungal infection of the nail beds	• Evidence of active infections, and other safety related exclusions • Known active infection of any kind (excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with IV anti infectives within 8 weeks of the screening visit or oral anti infectives within 2 weeks prior to the screening visit
Receipt of any of the excluded therapies below:	
• Any anti-CD20 therapy such as rituximab, ocrelizumab, or ofatumumab less than 9 months prior to screening or during screening • If an anti-CD20 therapy has been received between 9 and 12 months prior to screening, the peripheral CD19-positive B-cell count had to be $\geq$25 cells/μL • Cyclophosphamide, tacrolimus, cyclosporine, or voclosporin during the 2 months prior to screening or during screening • Any biologic therapy (other than anti-CD20) such as, but not limited to, belimumab, ustekinumab, anifrolumab, secukinumab, or atacicept during the 2 months prior to screening or during screening • Oral inhibitors of JAK, BTK, or TYK2, including baricitinib, tofacitinib, upadacitinib, filgotinib, ibrutinib, or fenebrutinib or any investigational agent during the 2 months prior to screening or during screening • Any live vaccine during the 28 days prior to screening or during screening	• Recent treatment with cyclophosphamide or calcineurin inhibitors (within 3 months), anti-CD20 targeted therapies (within 12 months), or a biologic B-cell targeted therapy other than anti-CD20 (within 6 months) • Previous treatment with an anti-CD20-targeted therapy within 12 months of randomization • Previous treatment with a biologic B-cell-targeted therapy (other than anti-CD20) within 6 months of randomization • Treatment with any investigational agent within 28 days of randomization or five half-lives of the investigational drug (whichever is longer) • Receipt of a live vaccine within 28 days of screening
Clinically significant bleeding	
High risk for clinically significant bleeding or any condition requiring plasmapheresis, IV immunoglobulin, or acute blood product transfusions	Unstable disease with thrombocytopenia or at high risk for developing clinically significant bleeding or organ dysfunction requiring therapies such as plasmapheresis or acute blood or platelet transfusions
Intolerance or contraindication to study therapies, including any shown below:	
• History of severe allergic or anaphylactic reactions to mAbs or known hypersensitivity to any component of the obinutuzumab infusion • Intolerance or contraindication to oral or IV corticosteroids • Intolerance to MMF • Lack of peripheral venous access	• History of severe allergic or anaphylactic reactions to mAbs or known hypersensitivity to any component of the obinutuzumab infusion • Intolerance or contraindication to oral or IV corticosteroids • Known intolerance to MMF and MPA • Lack of peripheral venous access

ACR = American College of Rheumatology; ANA = antinuclear antibody; BTK = Bruton's tyrosine kinase; CKD-EPI = Chronic Kidney Disease Epidemiology; eGFR = estimated glomerular filtration rate; EULAR = European League Against Rheumatism; ISN = International Society of Nephrology; IV = intravenous; JAK = Janus-associated kinase; mAbs = monoclonal antibodies; MMF = mycophenolate mofetil; MPA = mycophenolic acid; RPS = Renal Pathology Society; SLE = systemic lupus erythematosus; TYK2 = tyrosine kinase 2; UPCR = urine protein to creatinine ratio.

Treatments

Blinded Treatment (Up to Week 76 Visit)

After screening, eligible patients were randomized to receive obinutuzumab or placebo in a 1:1 ratio. Patients randomized to receive obinutuzumab were further randomized in a 1:1 ratio. Obinutuzumab 1000 mg or placebo were administered by intravenous (IV) infusion during blinded treatment at Day 1 and Weeks 2, 24, 26, 50, and 52. Obinutuzumab 1000 mg was administered by IV infusion during blinded treatment as follows:

- Obinutuzumab arm 1 (2-2-2 regimen): absolute (flat) dose of 1000 mg IV on Day 1 and Weeks 2, 24, 26, 50, and 52
- Obinutuzumab arm 2 (2-2-1 regimen): absolute (flat) dose of 1000 mg IV on Day 1 and Weeks 2, 24, 26, and 52

To preserve the treatment blind, patients in obinutuzumab arm 2 (2-2-1 regimen) received a placebo infusion at Week 50.

Beyond Week 76 Visit

After Week 76, patients may continue receiving blinded study treatment (obinutuzumab or placebo), enter OLT, and/or enter SFU.

Continue Blinded Study Treatment

Patients in either treatment arm who had an adequate response at Week 76 without a need for intensification of therapy or unmanageable treatment-emergent adverse events continue to receive blinded obinutuzumab 1000 mg or placebo infusions every 6 months beginning at Week 80, until study unblinding. An adequate response was present if all of the following criteria were met: urine protein to creatinine ratio (UPCR) $<$0.8 g/g or $\geq$50% reduction in UPCR from baseline to sub nephrotic levels (3 g/g), no deterioration in renal function from baseline (estimated glomerular filtration rate [eGFR] $\geq$85% of baseline), no need for high-dose corticosteroids, and no receipt of rescue therapy or treatment failure. The randomized treatment assignment was not revealed and investigators and patients remained blinded during this period. Background immunosuppression, including doses of corticosteroids and MMF, could be adjusted at the investigator's discretion beginning at Week 80.

Open-Label Treatment (OLT)

For patients with an inadequate treatment response at Week 76, OLT with obinutuzumab 1000 mg is provided if all the following criteria were met at Week 76:

- Inadequate treatment response
- Clinically meaningful improvement from baseline in renal parameters or prior clinically meaningful improvement from baseline followed by worsening

- Need for intensification of therapy
- No unmanageable treatment-emergent adverse events
- No rescue therapy (except corticosteroid-only rescue) or treatment failure.

OLT follows the initial obinutuzumab treatment schedule with infusions on OLT Day 1 and at OLT Weeks 2, 24, 26, 52, and once every 6 months thereafter. Patients who discontinue OLT enter SFU. Additionally, patients who, during blinded treatment after Week 80, experience a loss of adequate response requiring intensification of therapy and without unmanageable treatment-emergent adverse events may initiate OLT once 60 days have elapsed from the most recent obinutuzumab or placebo infusion.

Study Follow-up (SFU) All patients are followed through Week 76 and for at least 12 months from the last dose of obinutuzumab or placebo:

- Patients who discontinued infusions prior to Week 76 were instructed to complete all visits through Week 76 according to the original schedule of activities before entering SFU.
- Patients who did not continue blinded infusions or entered OLT based on the Week 76 assessment entered SFU.
- Patients who discontinue all infusions (blinded and open-label) beyond Week 76 will enter SFU. Investigators and patients remain blinded to treatment assignment during SFU. The first SFU visit is scheduled approximately 6 months after the previous study visit (e.g., 6 months after Week 76) and patients return for regular assessments every 6 months. Background immunosuppression, including MMF and corticosteroids, may be adjusted at the investigator's discretion. Patients who do not reach B cell recovery, defined as peripheral CD19-positive B cell count at the patient's lowest pretreatment level or 25 cells/μL CD19-positive count (the lower limit of normal [LLN] for this lupus population under study), whichever is lower, and who have not received a rescue therapy associated with reductions in peripheral B cells (e.g., rituximab, cyclophosphamide, or use of obinutuzumab outside the study protocol) will continue to be followed every 6 months. The follow-up visits will continue until any of the following occurs: return of peripheral CD19-positive B cells to the patient's lowest pretreatment value or achieving 25 cells/μL CD19-positive count, whichever is lower, or receipt of a therapy associated with reductions in peripheral B cells, or end of study.

Table 10 Premedications to Reduce the Risk of Infusion-Related Reactions (IRR) in REGENCY and NOBILITY

REGENCY	NOBILITY
For blinded infusions at Day 1 and Weeks 2, 24, 26, 50, and 52, the following premedications were administered and completed between 30 and 60 minutes prior to the obinutuzumab or placebo infusion: • Methylprednisolone 80 mg IV and • Acetaminophen (650–1000 mg) PO and • Diphenhydramine 50 mg PO or IV (or equivalent dose of a similar agent)	For blinded infusions at Day 1 and Weeks 2, 24, and 26, the following premedications were administered and completed between 30 and 60 minutes prior to the obinutuzumab or placebo infusion: • Methylprednisolone 80 mg IV or placebo methylprednisolone [a] and • Acetaminophen (650–1000 mg) PO and • Diphenhydramine 50 mg PO (or equivalent dose of a similar agent)

IV = intravenous; PO = orally.

[a] Prior to each infusion, patients randomized to obinutuzumab received methylprednisolone 80 mg IV and patients randomized to placebo received methylprednisolone placebo.

Table 11 ***Standard Therapies in REGENCY and NOBILITY***

REGENCY	NOBILITY
Antihypertensive Therapy	
• Either an ACE inhibitor or an ARB titrated to adequate blood pressure control as recommended by the KDIGO Blood Pressure Work Group for chronic kidney disease (Becker et al. 2012). • Patients should have been on either an ACE inhibitor or ARB for at least 10 days prior to randomization.	• During screening, every effort should have been made to adequately control patients' blood pressure. • Patients should have been on either an ACE inhibitor or ARB for at least 10 days prior to randomization.
Antimalarial Therapy	
• Should have been provided as background medication as was consistent with treatment guidelines and local clinical practice. • Should have been initiated prior to Day 1 and maintained at a constant dose through Week 80. • Suggested dose ranges were as follows: hydroxychloroquine (200–400 mg daily), chloroquine (500 mg daily or every other day), or quinacrine (100 mg daily).	• Patients taking antimalarial medications at study entry should have maintained a constant dosage throughout the study. • Patients not previously on antimalarial medications may have been enrolled in the study but should not have initiated antimalarial medications unless experiencing a disease flare that was unresponsive to corticosteroids.
Mycophenolate Mofetil (MMF) or Mycophenolic Acid (MPA)	
• MMF was titrated by Week 4 to target dose of 2.0-2.5 g/day in divided doses. • MMF was maintained at the target dose through Week 80.	• All patients continued or initiated either MMF or MPA during screening or no later than Day 1. • MMF or MPA was given in two or three divided doses and titrated by Week 4 to 2.0–2.5 g/day for MMF or 1440–1800 mg/day for MPA.
Oral Prednisone	
Oral prednisone was initiated at 0.5 mg/kg (maximum 60 mg/day) until Day 15 and tapered to a total daily maintenance dose of 5 mg/day by Week 24 and maintained at this dose until Week 80.	Oral prednisone was initiated at 0.5 mg/kg (maximum 60 mg/day) and tapered over 10 weeks to a daily maintenance dose of 7.5 mg/day by Week 12 and maintained at this dose until Week 52.
Methylprednisolone Pulse Therapy	

REGENCY	NOBILITY
• Methylprednisolone 250-1000 mg IV (prior to or during screening or on Day 1 prior to first infusion of study treatment) was administered. • During the 6 months prior to screening, during screening, or on Day 1 (prior to the first infusion of study treatment), all patients must have received at least one pulse-dose methylprednisolone IV (250–1000 mg) or equivalent for the treatment of the current episode of active lupus nephritis. • The maximum permitted dose of pulse corticosteroids during the 4 weeks prior to screening or during screening was 3 g methylprednisolone IV or equivalent.	• Methylprednisolone 1000 mg IV (prior to or during screening) was administered. • It was permitted to receive up to a total of 3000 mg methylprednisolone IV prior to randomization for severe clinical activity according to the guidelines of routine care for these patients.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; IV = intravenous; KDIGO = Kidney Disease: Improving Global Outcomes; MMF = mycophenolate mofetil; MPA = mycophenolic acid.

Objectives and outcomes/endpoints

Table 12 Objectives and endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective	
• To evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo	• Proportion of patients who achieved a CRR at Week 76, with CRR defined as achievement of all of the following: – UPCR < 0.5 g/g – 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
Secondary (Key) Efficacy Objectives [b]	
• To evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo	• Proportion of patients who achieved CRR with successful prednisone taper at 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 • Proportion of patients who achieved a proteinuric response at Week 76, with proteinuric response 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 • Mean change in eGFR from baseline to Week 76 • Proportion of patients who experienced death or renal-related events through Week 76, defined as the proportion of patients with one or more of the following events: – Death – Treatment failure [c] – 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

• To evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo	• Proportion of patients who achieved an ORR, defined as achievement of either CRR or PRR, evaluated at Week 50, with PRR defined as achievement of all of the following: – ≥ 50% reduction in UPCR from baseline – UPCR < 1g/g (or < 3 g/g if the baseline UPCR was ≥ 3 g/g) – 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
Supportive Secondary Efficacy Objectives	
• To evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo	• Change in anti-dsDNA titer from baseline to Week 50 • Change in C3 from baseline to Week 50 • Change in SLEDAI-2K from baseline to Week 76 • Time to onset of CRR over the course of 76 weeks • Proportion of patients who achieved CRR with serum creatinine criteria at Week 76, with CRR with serum creatinine criteria defined as achievement of all of the following: – UPCR < 0.5 g/g – Serum creatinine ≤ ULN (as determined by the central laboratory) – Serum creatinine not increased from baseline by > 25% – No occurrence of the following intercurrent events [a]: Rescue therapy, treatment failure, death, or early study withdrawal

Exploratory Efficacy Objectives	
• To evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo	• Proportion of patients who achieved the individual components of CRR at Week 76: – UPCR < 0.5 g/g – 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 • Proportion of patients who achieved CRR on the randomized, blinded therapy at Weeks 106, 132, 158, 184, and 210 [d] • Proportion of patients who achieve proteinuric response on the randomized, blinded therapy at Weeks 106, 132, 158, 184, and 210 [d] • Proportion of patients who achieve ORR on the randomized, blinded therapy at Weeks 106, 132, 158, 184, and 210 [d] • Proportion of patients who achieved CRR at Week 76, as defined as achievement of all of the following: – UPCR < 0.5 g/g – eGFR ≥ 85% of baseline, as calculated using the CKD-EPI equation or ≥ 60 mL/min per 1.73 m^2 of body-surface area – No occurrence of the following intercurrent events [a]: Rescue therapy, treatment failure, death, or early study withdrawal • Proportion of patients who receive rescue therapy or experience treatment failure by Week 76 • Change in anti-dsDNA titer from baseline to Weeks 4, 12, 24, and 76 • Change in C3 from baseline to Weeks 4, 12, 24, and 76 • Change in C4 from baseline to Weeks 4, 12, 24, 50, and 76 • Change in UPCR from baseline to Weeks 24, 50, and 76 • Change in eGFR slope from Week 12 to Week 76

Objectives	Corresponding Endpoints
• To evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo	• Time to LN flare from Week 24, 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; or – Receipt of rescue therapy, except for corticosteroid-only rescue. • Time to an unfavorable kidney outcome, defined as the first of the following events: treatment failure, serum creatinine doubling, or death • Change in Physician's Global Assessment from baseline to Weeks 24, 50, and 76 • Change in Subject's Global Assessment from baseline to Weeks 24, 50, and 76

ADA=anti-drug antibody; anti-dsDNA=anti–double-stranded DNA; CI=confidence interval; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CMH=Cochrane-Mantel-Haenszel; CRR=complete renal response; eGFR=estimated glomerular filtration rate; EQ 5D-5L=EuroQol 5 Dimension, 5-Level Questionnaire; HRQoL=health-related quality of life; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=overall renal response; PD=pharmacodynamic; PK=pharmacokinetic; PRR=partial renal response; SF-36 v2=Short Form Survey, Version 2; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; ULN=upper limit of normal; UPCR=urinary protein-to-creatinine ratio; VAS=visual analog scale.

Note: some exploratory endpoints are discussed in the Protocol, Section 2.1 and the SAP, Section 1.1.1.3, but are not analyzed at the time of this report.

[a] Intercurrent events for the study are the following: rescue therapy, treatment failure, study treatment discontinuation, death, and early study withdrawal.

[b] Note that key secondary endpoints are presented in the sequence for endpoint testing as described in Section 3.7.3.2.

[c] 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 (c) receipt of rescue therapy, except for corticosteroid–only rescue.

[d] Of note, as of the CCOD (15 August 2024) for this Clinical Study Report, no patient had reached their Week 210 visit; therefore, no Week 210 results are presented herein.

Sample size

The primary efficacy endpoint of this study is the proportion of patients who achieve CRR. Based on the Phase II NOBILITY trial, it is estimated that approximately 30% of patients with proliferative LN who are receiving MMF will achieve CRR at Week 76 and that the addition of obinutuzumab to MMF will induce an overall CRR rate of 50% at Week 76. On the basis of these assumptions, a total of 252 patients randomized to obinutuzumab and placebo groups in a 1:1 ratio (126 patients in each of the obinutuzumab- and placebo-treated groups) stratified by region and race will yield approximately 90% power to compare the combined obinutuzumab treatment group with the placebo group at the two-sided $\alpha=0.05$ significance level using a Cochrane-Mantel-Haenszel (CMH) test, assuming the same CRR proportions across the strata.

Randomisation

The investigator or the investigator's research staff provided patient eligibility information through the interactive Web response system (IxRS) at randomization. Each patient was randomized and assigned a unique identification number. As confirmation, the investigator was provided with written verification of each patient's registration. Patients were randomized to receive obinutuzumab or placebo in a 1:1 ratio.

The randomization of patients into treatment and control groups was managed by a central IxRS vendor and performed by stratified block design–stratified by region (United States and Canada**;** Latin America and the Caribbean; or Other) and race (Black; or Other).

These stratification factors were selected given expected differences in response by region and race. LN is clinically heterogeneous in presentation and factors such as availability and intensity of standard of care therapies; socioeconomic status; and ethnicity are known to affect a patient's response to treatment. In particular, black race is associated with more aggressive disease.

Blinding (masking)

The study consists of the following four periods: screening, blinded treatment, open-label treatment (OLT), and study follow-up (SFU). Because it is important to maintain blinding to preserve the integrity of the data collected, all laboratory studies of blood specimens, with unblinding potential, were performed by a central laboratory. Therefore, site personnel and the Sponsor's staff involved with the conduct of the study did not receive unblinded data related to peripheral B-cell counts, PK results, specific immunoglobulin levels, or ADA results during the study, as listed below, until the primary efficacy and safety analyses through Week 76. While PK samples were collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients were generally, not needed for the safe conduct or proper interpretation of this study. Sponsor personnel responsible for performing PK assays were unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients who were assigned to the comparator arm were not analyzed except by request (e.g., to evaluate a possible error in dosing).

If emergency unblinding was necessary for patient management (e.g., in the case of a SAE for which patient management might be affected by knowledge of treatment assignment), the investigator was able to break the treatment code by contacting the IxRS. Treatment codes were not to be broken except in emergency situations. If the investigator wished to know the identity of the study treatment for any other reason, he or she had to contact the Medical Monitor directly. The investigator would document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to an SAE).

No Independent Review Facility was planned for this study. An independent Data Monitoring Committee (iDMC) was used to monitor study data on an ongoing basis.

Statistical methods

Analysis sets

Randomized Population

The randomized population includes all patients randomized into the study.

Evaluable Population

Efficacy-evaluable population consists of all randomized patients regardless of whether they received study drug. Patients are grouped according to randomized (assigned) treatment, rather than treatment

received. Patients who received an incorrect therapy are reported under the treatment group to which they were randomized.
All efficacy analyses were performed using the efficacy-evaluable population.

Safety-Evaluable Population

The safety-evaluable population is defined as patients who received any part of blinded infusion of obinutuzumab or placebo. Patients who were randomized to the study but who did not receive any part of blinded infusion of obinutuzumab or placebo are not included in the safety population. Patients are grouped according to the treatment that patients 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 group at randomization are reported under the obinutuzumab treatment group.

All safety analyses were performed using the safety-evaluable population.

Pharmacokinetic-Evaluable Population

The pharmacokinetic-evaluable population (PK population) include all patients who have been randomized to and received any dose of obinutuzumab given as study medication, have at least one post-dose PK sample that is evaluable.

Statistical analysis

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients who achieve CRR, evaluated at Week 76.

A patient was considered a responder for CRR if the following conditions are met:

- UPCR<0.5 g/g
- 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

The primary estimand attributes are as follows:

- Population: patients with active or active/chronic ISN/RPS 2003 Class III or IV proliferative lupus nephritis
- Primary endpoint (variable): CRR
- Treatments: Experimental: obinutuzumab 1000 mg IV infusion at Day 1 and Weeks 2, 24, 26, and either Weeks 50 and 52 or Week 52 only. Control: placebo
- Intercurrent events: rescue therapy, treatment failure, study treatment discontinuation, death or early study withdrawal. Handling of intercurrent events: Rescue therapy, treatment failure, death and early study withdrawals are addressed in the endpoint definition and are handled under the composite variable strategy. Study treatment discontinuation are handled using treatment policy strategy.
- Summary measure: difference in proportion at Week 76. The proportions of patients achieving CRR across obinutuzumab (combined treatment groups) and placebo groups were compared using a CMH test with region (United States and Canada vs. Latin America and the Caribbean vs. other) and race (Black vs. other) as stratification factors. The hypothesis test is conducted at 5% level of significance (two-sided). Serum creatinine (used to calculate eGFR) and 24-hour UPCR data obtained from the central laboratory are used for efficacy analysis. eGFR is calculated using the CKD-EPI equation. If the baseline eGFR data is missing, then it is imputed by the screening value.

Missing data imputation was performed by multiple imputations using data from patients who did not experience the intercurrent events that are handled using composite strategy, i.e., rescue therapy, treatment failure, death, and early study withdrawal. Prior to applying multiple imputations, missing 24-hour UPCR at any visit was first imputed by Spot UPCR. Missing UPCR (when both 24-hour and spot UPCR are missing) and eGFR data for the primary endpoint CRR at Week 76 was imputed by fully conditional specification (FCS) predicted mean matching method. This is also known as multivariate imputation by

chained equations (MICE). A set of candidate donors with 5 members is chosen for the predictive mean matching method. Separate imputation models were used for each treatment arm. Only patients who did not experience the intercurrent events that are handled using the composite strategy, i.e., rescue therapy, treatment failure, death, and early study withdrawal, were included in the imputation model.

UPCR and eGFR were imputed using a single imputation model. The imputation model specified UPCR at Week 76 as the dependent variable and will include eGFR at Week 76 as an auxiliary variable to be imputed as part of the MICE procedure. UPCR and eGFR at Week 24, 36, 50, 64 and 76 was used in the analysis. As 24-hour UPCR is not collected at Weeks 36 and 64, spot UPCR was used in the models for these time points.

Sensitivity Analyses for Primary Endpoint

A sensitivity analysis of the primary endpoint was performed using the following missing data imputation technique:
eGFR: Missing eGFR at Week 76 was imputed from the eGFR at Week 64.
UPCR: If the 24-hour UPCR at Week 76 is missing, then it was imputed in the following order:

- Spot UPCR at Week 76
- Spot UPCR at Week 64

If any of the components for CRR are still missing after the above imputation rules are applied, then the patient was set to non-responder.

Other Supplementary Analyses for Primary Endpoint

Analysis with Early Study Withdrawals Being Handled as Missing Data

An analysis was performed with a different strategy to handle early study withdrawals. Early study withdrawal was not considered as an intercurrent event. Patients who withdraw early from the study will be considered as having missing data after their withdrawal.

The estimand attributes for the analysis were as follows:
Population: Patients with active or active/chronic ISN/RPS 2003 Class III or IV proliferative lupus nephritis
Endpoint (variable): CRR. A patient will be considered a responder for CRR if the following conditions are met at the Week 76 visit:
– UPCR <0.5
– EGFR ≥85% of baseline, as calculated using the CKD-EPI equation
– No occurrence of rescue therapy, treatment failure, or death prior to Week 76
Treatments: – Experimental: Obinutuzumab 1000 mg IV infusion at Day 1 and Weeks 2, 24, 26, and either Weeks 50 and 52 or Week 52 only
– Control: Placebo
Intercurrent events: Rescue therapy, treatment failure, study treatment discontinuation, or death prior to Week 76. Rescue therapy, treatment failure, and death are addressed in the endpoint (variable) definition and are handled under the composite strategy.

Study treatment discontinuation would be handled using treatment policy strategy. Summary measure: Difference in proportions at Week 76 Treatment Policy Strategy
Primary endpoint was to be analyzed using treatment policy strategy to handle the intercurrent events: rescue therapy, treatment failure, and study treatment discontinuation. Death was to be handled using composite strategy. Patients who withdraw early from the study were to be considered as having missing data after their withdrawal. Missing data were to be imputed by multiple imputations using the same approach considered in the primary analysis. Only patients who did not experience death were to be included in the imputation model.

Tipping Point Analysis

A tipping point analysis was performed to explore the plausibility of the missing data assumptions (i.e. Missing At Random [MAR]). The TP analysis varied assumptions about missing outcomes for the two treatment arms independently, to explore scenarios under which there is no longer evidence of treatment

effect. This analysis would target the estimand of the supplementary analysis based on the treatment policy strategy above.
The response values for participants with missing CRR would be imputed deterministically, exploring all possible responder/non-responder combinations across treatment arms. In each unique scenario, a Pearson's chi-squared test would be implemented to assess the treatment effect given the imputed response values in each respective scenario. The stratification factors used in the main analysis was disregarded and an unstratified analysis will be carried out within the TP analysis. The only foreseen impact of carrying out an unstratified analysis was that conclusions would be slightly more conservative.

For each unique scenario, a corresponding P-value from the Pearson's chi-squared test would be obtained, providing a result of statistical significance, at a level of 0.05. These results would be plotted on a grid, with the x- and y-axes representing the number of participants who were imputed as responders for the placebo and obinutuzumab arms respectively. The region on the produced plot where the conclusion changes (significant to non-significant, P<0.05 to P≥0.05) would be interpreted as the tipping point.

Subgroup Analyses for Primary Endpoint
The generalizability of CRR results when comparing obinutuzumab group to placebo group would be investigated by estimating the treatment effect in subgroups based on the following baseline factors:

- Region (United States and Canada vs. Latin America and the Caribbean vs. other)
- Race (black vs. other)
- Sex
- UPCR (≥3 vs. <3)
- anti-dsDNA (>120 IU/mL vs. ≤120 IU/mL)
- C3 (<0.9 g/L vs. ≥0.9 g/L)
- C4 (<0.1 g/L vs. ≥0.1 g/L)
- Class III versus Class IV LN
- Concomitant Class V LN
- Prior history of LN (Yes/No)
- eGFR (<30 vs. 30-<60 vs. 60-<90 vs. ≥90 mL/min/1.73 m2)

Key Secondary Efficacy Endpoints
The key secondary efficacy endpoints were the followings:

- Proportion of patients who achieve a proteinuric response at Week 76.

Proteinuric response is defined as achievement of all of the following: UPCR < 0.8 g/g and no occurrence of *the following* intercurrent events:
-Rescue therapy, treatment failure, *death* or early study withdrawal
-Proportion of patients who achieve CRR with successful prednisone taper at
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

- Proportion of patients who achieve an ORR, defined as achievement of either CRR or PRR, evaluated at Week 50

PRR is defined as achievement of all of the following:
– ≥ 50% reduction in UPCR from baseline
– UPCR < 1 (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

- Proportion of patients who experience death or renal-related events through Week 76, defined as the proportion of patients with one or more of the following events:

– Death
– Treatment failure
– Worsening proteinuria, defined as a confirmed ≥ 50% increase in UPCR to a value ≥ 3
– Worsening eGFR, define as a confirmed ≥ 30% decrease in eGFR to a value < 60

- Mean change in eGFR from baseline to Week 76

- Change in FACIT-F scale from baseline to Week 76

All the key secondary endpoints were compared between obinutuzumab (combined treatment groups) and placebo groups. Proteinuric response, ORR and death or renal related event were analyzed similarly as the primary endpoint using a CMH test. Change from baseline in eGFR *and FACIT-F scale* were analyzed by appropriate methods derived from estimand attributes and will be specified in the SAP.
To control for multiple comparisons, the primary and key secondary endpoints were tested in a pre-specified order at a two-sided 0.05 significance level. The order of testing *and multiplicity control method* were pre-specified in the SAP and finalized prior to database lock for the primary analysis.
Sensitivity analyses were performed to assess the potential impact on the primary endpoint, and possibly also key secondary endpoints, of missing data and possibly also changes to background immunosuppressive medication.

Supportive Secondary Efficacy Endpoints

The supportive secondary efficacy endpoints are listed below:

- Change in anti-dsDNA titer from baseline to Week 50
- Change in C3 from baseline to Week 50
- Change in SLEDAI-2K from baseline to Week 76
- Time to onset of CRR over the course of 76 weeks
- Proportion of patients who achieve CRR with serum creatinine criteria at Week 76

CRR with serum creatinine criteria is defined as achievement of all of the followings:
– UPCR < 0.5
– Serum creatinine ≤ ULN (upper limit of normal, as determined by the central laboratory)
– Serum creatinine not increased from baseline by > 25%
- No occurrence of *the following* intercurrent events: Rescue therapy, treatment failure, death or early study withdrawal

All the supportive secondary efficacy endpoints were compared between obinutuzumab (combined treatment groups) and placebo groups. CRR with serum creatinine criteria were analyzed similarly as the primary endpoint using a CMH test.

Multiplicity

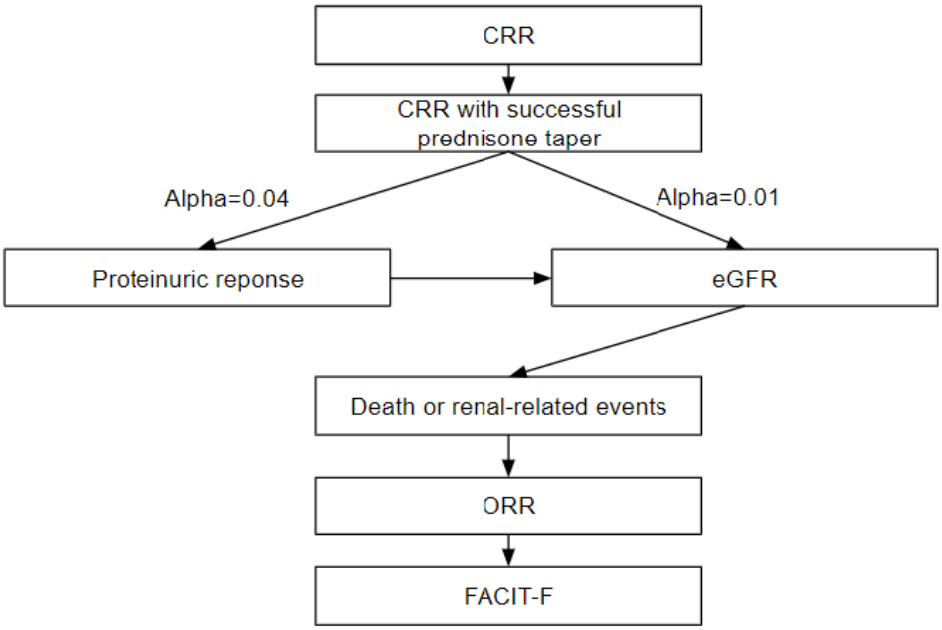
Secondary endpoints were tested to compare obinutuzumab (combined treatment groups) with placebo groups for the superiority of obinutuzumab over placebo. To control the overall type I error, a fallback method maintaining a fixed sequence for testing was used.

The sequence for endpoint testing was the primary endpoint, followed by key secondary endpoints in the following order:
1. Proportion of patients who achieve CRR with successful prednisone taper at Week 76
2. Proportion of patients who achieve a proteinuric response at Week 76
3. Change in eGFR from baseline to Week 76

If the primary endpoint test was significant at two-sided alpha level 0.05, the first key secondary endpoint in the sequence, CRR with successful prednisone taper, would be tested at alpha level 0.05.
If the CRR with successful prednisone taper was not significant, the testing stops and the endpoints after it in the sequence would be deemed non-significant. If the CRR with successful prednisone taper was significant, the alpha 0.05 would be split as 0.04 and 0.01 to the next two endpoints, the proteinuric response and the change in eGFR, respectively.
If the proteinuric response endpoint was significant at 0.04 alpha level, this alpha was unused and would be passed to the change in eGFR endpoint giving a total alpha for the change in eGFR endpoint test of 0.05 (0.01+0.04). The change in eGFR endpoint test would then be performed at alpha level 0.05.
If the proteinuric response endpoint was not significant at level 0.04, the change in eGFR endpoint would be tested at the originally reserved alpha of 0.01.
If the change in eGFR was not significant at either 0.05 or 0.01 depending on whether the proteinuric response endpoint was significant, the testing would stop.
If the change in eGFR was significant, the unused alpha (either 0.05 or 0.01 depending on whether the proteinuric response endpoint was significant) would be passed to the next endpoints in the sequence and each endpoint would be tested sequentially after achieving the statistical significance on the previous endpoint.

Testing stoped as soon as there was a failure of an endpoint in the following sequence to show significance. The endpoints after the non-significant endpoint in the sequence would be deemed non-significant.
4. Proportion of patients who experience death or renal-related events through Week 76
5. Proportion of patients who achieve an ORR evaluated at Week 50
6. Change in FACIT-F scale from baseline to Week 76 The fallback method described above is also depicted in Figure 24.

Figure 28 Multiplicity adjustement using fallback method



Protocol amendments

There have been 4 protocol amendments to the original Protocol CA41705, Version 1, which was released on 23 December 2019. A summary of key changes to the protocol is provided below:

Version 2: Dated 10 March 2020

- In response to recommendations from the U.S. Food and Drug Administration (FDA), the obinutuzumab treatment arm was split into two groups:
    - Obinutuzumab arm 1 (2-2-2 regimen) received obinutuzumab 1000 mg IV infusions on Day 1 and Weeks 2, 24, 26, 50, and 52
    - Obinutuzumab arm 2 (2-2-1 regimen) received obinutuzumab 1000 mg IV infusions on Day 1 and Weeks 2, 24, 26, and 52.

  Comparison of these two obinutuzumab dosing groups will provide additional data to support the appropriate dose of obinutuzumab for use in the chronic treatment of lupus nephritis. The sample size for the study was increased to 252 patients to permit randomization into the three groups, and the study schema was updated.
- The primary efficacy objective was changed to compare the combined obinutuzumab treatment groups with placebo on achievement of CRR at Week 76. Secondary and exploratory objectives were also revised to reflect the comparison of the combined obinutuzumab treatment groups with placebo.
- An exploratory descriptive comparison of the obinutuzumab subgroups at Week 76 was added.

- A Week 50 infusion visit was added for all patients. Patients not receiving obinutuzumab 1000 mg IV at this visit received placebo. All Week 52 assessments and endpoints were moved to Week 50 to permit these assessments to occur prior to Month 12 infusions.
- Stratification factors were revised to include region (United States and Canada vs. Latin America and the Caribbean vs. other) and race (Black vs. other).
- The list of intercurrent events was updated to include early withdrawal instead of study treatment discontinuation as an intercurrent event. This change removed the previous requirement that patients who discontinued study treatment but completed study assessments be treated as nonresponders.
- Lack of response to 2 weeks of corticosteroids following the occurrence of a flare was removed from the criteria for treatment failure. This change was made to permit investigators to make a clinical determination about the suitability of continuing blinded infusions based on clinical judgement, the severity of the patient's flare, and the patient's change in renal parameters from baseline.
- Corticosteroid rescue, defined as receipt of pulse steroids or sustained use of highdose corticosteroids after Week 52, was defined. Patients who received corticosteroid rescue were treated as nonresponders.
- Worsening of pre-existing cardiac conditions was added as a potential risk associated with obinutuzumab, and an adverse event of special interest to be consistent with other obinutuzumab protocols.

Version 3: Dated 23 April 2021

- Renal criteria for the primary endpoint, complete renal response, were revised to the following: eGFR ≥85% of the baseline value, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
- Secondary endpoint renal function criteria were updated, and new secondary endpoints (proteinuric response at Week 76 and proportion of patients who experience death or renal-related events through Week 76) were introduced. Additionally, key versus supportive secondary endpoints were identified, and method of controlling type I error rate was updated.
- Exploratory endpoints were updated to align with primary and secondary endpoints.
- The end of study was defined as a maximum of 18 months from the last obinutuzumab infusion (blinded and open-label) administered.

Version 4: Dated 14 March 2023

- The exploratory endpoint "proportion of patients who achieve CRR with successful prednisone taper at Week 76, defined as achievement of CRR with no receipt of prednisone >7.5 mg/day (or equivalent) from Week 64 through Week 76" was promoted to a key secondary endpoint.
- A new exploratory endpoint, defined as achievement of CRR with no receipt of prednisone >7.5 mg/day (or equivalent) from Week 52 through Week 76, was added.
- The end of the study after the last patient is enrolled was corrected to 5 years, and the total length of the study was corrected to 8 years.
- Description of a newly identified potential risk of coagulation abnormalities in patients receiving obinutuzumab, including disseminated intravascular coagulation, was added.

Version 5: Dated 7 February 2024

- "Change in Functional Assessment of Chronic Illness Therapy−Fatigue scale from baseline to Week 76" was promoted from supportive secondary efficacy endpoint to key secondary endpoint, to reflect the high relevance of fatigue from a patient's perspective.
- "Proportion of patients who achieve CRR at Week 76," as defined by achievement of all of the following: UPCR the CKD-EPI equation; or ≥60 mL/min per 1.73 mL2 of body-surface area, was added as an exploratory endpoint.
- "Estimated glomerular filtration rate (eGFR) slope from Week 12 to Week 76" was added as an exploratory efficacy objective as a predicter of future risk of ESKD.
- "Time to an unfavourable kidney outcome, defined as the first of the following events: treatment failure, serum creatinine doubling, or death" was added as an exploratory efficacy objective.
- Efficacy-evaluable analysis set was updated to include all randomized patients regardless of whether they received study treatment, in response to health authority feedback on the statistical analysis plan.
- Intercurrent events of the primary endpoint were updated, in response to health authority feedback on the statistical analysis plan. Study treatment discontinuation was added as an intercurrent event to be handled with treatment policy strategy; death was specified as an intercurrent event. A full list of changes to the protocol, including the rationale for each change, is provided in the Protocol Amendment Rationale in the final protocol (Protocol Version 5, Amendment Rationale).

Results

Participant flow

Table 13 Patient disposition at CCOD (randomized patients)

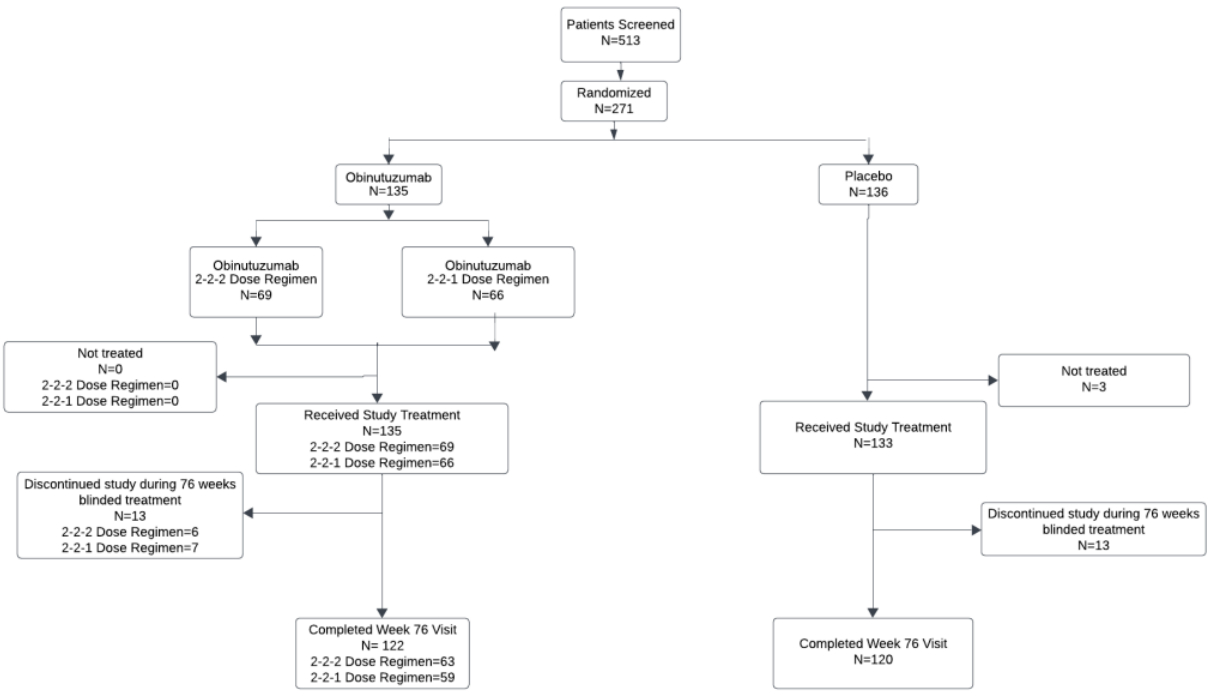


Table 14 Patient disposition at CCOD (randomized patients)

	Obinutuzumab (N=135)	Placebo (N=136)	All Patients (N=271)
Completed study	0	0	0
Discontinued study	19 (14.1%)	34 (25.0%)	53 (19.6%)
Adverse event	1 (0.7%)	1 (0.7%)	2 (0.7%)
Death	5 (3.7%)	4 (2.9%)	9 (3.3%)
Lack of efficacy	1 (0.7%)	2 (1.5%)	3 (1.1%)
Lost to follow-up	1 (0.7%)	2 (1.5%)	3 (1.1%)
Non-compliance with study drug	1 (0.7%)	0	1 (0.4%)
Other	0	5 (3.7%)	5 (1.8%)
Physician decision	0	6 (4.4%)	6 (2.2%)
Withdrawal by subject	10 (7.4%)	14 (10.3%)	24 (8.9%)
Ongoing study	116 (85.9%)	102 (75.0%)	218 (80.4%)
Ongoing in blinded treatment after Week 76 period	67 (49.6%)	49 (36.0%)	116 (42.8%)
Ongoing in open label treatment period	26 (19.3%)	35 (25.7%)	61 (22.5%)
Ongoing in study follow-up period	23 (17.0%)	18 (13.2%)	41 (15.1%)

CCOD = Clinical Cut-Off Date.
Includes data collected on or before CCOD.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Table 15 Reasons for study discontinuation during 76-week blinded treatment period (randomized patients)

	Obinutuzumab (N=135)	Placebo (N=136)	All Patients (N=271)
Discontinued study during 76 weeks blinded treatment period	13 (9.6%)	16 (11.8%)	29 (10.7%)
Adverse event	0	1 (0.7%)	1 (0.4%)
Death	3 (2.2%)	1 (0.7%)	4 (1.5%)
Lost to follow-up	0	1 (0.7%)	1 (0.4%)
Non-compliance with study drug	1 (0.7%)	0	1 (0.4%)
Other	0	2 (1.5%)	2 (0.7%)
Physician decision	0	5 (3.7%)	5 (1.8%)
Withdrawal by subject	9 (6.7%)	6 (4.4%)	15 (5.5%)

Includes data through 76 weeks blinded treatment period.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Table 16 Reasons for study discontinuation from blinded Obinutuzumab infusions (safety-evaluable patients)

	Obinutuzumab (N=136)	Placebo (N=132)	All Patients (N=268)
Discontinued blinded Obinutuzumab treatment up to Week 76	29 (21.3%)	38 (28.8%)	67 (25.0%)
Adverse event	7 (5.1%)	2 (1.5%)	9 (3.4%)
Death	3 (2.2%)	1 (0.8%)	4 (1.5%)
Lack of efficacy	6 (4.4%)	22 (16.7%)	28 (10.4%)
Other	2 (1.5%)	2 (1.5%)	4 (1.5%)
Physician decision	4 (2.9%)	6 (4.5%)	10 (3.7%)
Pregnancy	2 (1.5%)	0	2 (0.7%)
Withdrawal by subject	5 (3.7%)	5 (3.8%)	10 (3.7%)

All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Table 17 Patients discontinued from blinded obinutuzumab infusions pre-week 52 infusion and post-week 52 infusion up to Week 76 by Obinutuzumab dose regimen, safety-evaluable patients in Regency

	Obinutuzumab Arm 1 (2-2-2 Regimen) (N=69)	Obinutuzumab Arm 2 (2-2-1 Regimen) (N=67)	Placebo (N=132)	All Patients (N=268)
Discontinued blinded Obinutuzumab treatment pre Week 52 infusion	8 (11.6%)	9 (13.4%)	22 (16.7%)	39 (14.6%)
Adverse event	3 (4.3%)	3 (4.5%)	2 (1.5%)	8 (3.0%)
Death	0	2 (3.0%)	1 (0.8%)	3 (1.1%)
Lack of efficacy	2 (2.9%)	0	15 (11.4%)	17 (6.3%)
Physician decision	0	2 (3.0%)	1 (0.8%)	3 (1.1%)
Pregnancy	1 (1.4%)	0	0	1 (0.4%)
Withdrawal by subject	2 (2.9%)	2 (3.0%)	3 (2.3%)	7 (2.6%)
Discontinued blinded Obinutuzumab treatment post Week 52 infusion up to Week 76	4 (5.8%)	8 (11.9%)	16 (12.1%)	28 (10.4%)
Adverse event	0	1 (1.5%)	0	1 (0.4%)
Death	0	1 (1.5%)	0	1 (0.4%)
Lack of efficacy	1 (1.4%)	3 (4.5%)	7 (5.3%)	11 (4.1%)
Other	1 (1.4%)	1 (1.5%)	2 (1.5%)	4 (1.5%)
Physician decision	0	2 (3.0%)	5 (3.8%)	7 (2.6%)
Pregnancy	1 (1.4%)	0	0	1 (0.4%)
Withdrawal by subject	1 (1.4%)	0	2 (1.5%)	3 (1.1%)

If a patient has not received an infusion at Week 52, it is assumed they discontinued treatment prior to Week 52 infusion.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Recruitment

First patient randomised: 10 AUG 2020

Last patient randomised: 02 MAR 2023

Clinical cut-off date: 15 AUG 2024

Conduct of the study

Table 18 Major protocol deviations (randomized patients)

Category Description	Obinutuzumab (N=135)	Placebo (N=136)	All Patients (N=271)
Total number of patients with at least one major protocol deviation	59 (43.7%)	50 (36.8%)	109 (40.2%)
Total number of major protocol deviations	95	94	189
EXCLUSION CRITERIA			
Greater than 50% of glomeruli with sclerosis	1 (0.7%)	1 (0.7%)	2 (0.7%)
Intolerance or contraindication to study therapies	1 (0.7%)	1 (0.7%)	2 (0.7%)
Recent major episode of infection as define in exclusion criteria	0	1 (0.7%)	1 (0.4%)
INCLUSION CRITERIA			
Baseline disease requirements not met	0	1 (0.7%)	1 (0.4%)
Failure to obtain informed consent	1 (0.7%)	1 (0.7%)	2 (0.7%)
Failure to re-consent on new version of the ICF	4 (3.0%)	5 (3.7%)	9 (3.3%)
Failure to receive pulsed solumedrol during 6 mos prior to SCR or during SCR	3 (2.2%)	0	3 (1.1%)
MEDICATION			
Exceeding protocol defined infusion rate limits	3 (2.2%)	5 (3.7%)	8 (3.0%)
Failure to document study drug administration	7 (5.2%)	7 (5.1%)	14 (5.2%)
Failure to securely control the study product	1 (0.7%)	1 (0.7%)	2 (0.7%)
Not administering mandatory prophylactic pretreatm	2 (1.5%)	2 (1.5%)	4 (1.5%)
Participant received study drug kit assigned to different participant	1 (0.7%)	0	1 (0.4%)
Received incorrect study medication	15 (11.1%)	15 (11.0%)	30 (11.1%)
Received prohibited concomitant medication	3 (2.2%)	3 (2.2%)	6 (2.2%)
PROCEDURAL			
AE's not assessed at each visit	0	2 (1.5%)	2 (0.7%)
Failure to follow a Safety Monitoring Plan	5 (3.7%)	3 (2.2%)	8 (3.0%)
Failure to follow the approved study procedure	11 (8.1%)	13 (9.6%)	24 (8.9%)
Failure to report SAE within 24 hours	10 (7.4%)	8 (5.9%)	18 (6.6%)
Missing required screening/baseline analyt. test	1 (0.7%)	2 (1.5%)	3 (1.1%)
No or incompl. haematol. & blood chemistry panel	0	1 (0.7%)	1 (0.4%)
No or incompl. vital signs or phys exam	2 (1.5%)	0	2 (0.7%)
Omitted study procedure(s) or entire visit	1 (0.7%)	3 (2.2%)	4 (1.5%)
Study procedure conducted out of timeframe	2 (1.5%)	0	2 (0.7%)
Study visit out of timeframe outlined in protocol	1 (0.7%)	1 (0.7%)	2 (0.7%)
Subject Enrollment before IRB approval	0	1 (0.7%)	1 (0.4%)
Unblinding of blinded site staff	1 (0.7%)	1 (0.7%)	2 (0.7%)

Percentages are of the total number of patients in the analysis population, as given in the column headings.
For frequency counts by deviation, multiple occurrences of the same deviation in an individual are counted only once.
For the total number of deviations, multiple occurrences of the same deviation in an individual are counted separately.
Includes major protocol deviations through 76 weeks blinded treatment period.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Baseline data

Table 19 Demographics (efficacy-evaluable patients)

	Obinutuzumab (N=135)	Placebo (N=136)	All Patients (N=271)
Age (yr)			
n	135	136	271
Mean (SD)	33.0 (10.5)	32.7 (10.0)	32.9 (10.2)
Median	30.0	31.0	31.0
Min - Max	18 - 64	18 - 72	18 - 72
Age group (yr)			
n	135	136	271
<65	135 (100%)	135 (99.3%)	270 (99.6%)
>=65	0	1 (0.7%)	1 (0.4%)
Sex			
n	135	136	271
Male	21 (15.6%)	21 (15.4%)	42 (15.5%)
Female	114 (84.4%)	115 (84.6%)	229 (84.5%)
Ethnicity			
n	135	136	271
Hispanic or Latino	71 (52.6%)	85 (62.5%)	156 (57.6%)
Not Hispanic or Latino	54 (40.0%)	48 (35.3%)	102 (37.6%)
Not Stated	9 (6.7%)	1 (0.7%)	10 (3.7%)
Unknown	1 (0.7%)	2 (1.5%)	3 (1.1%)
Race			
n	135	136	271
American Indian or Alaska Native	25 (18.5%)	26 (19.1%)	51 (18.8%)
Asian	9 (6.7%)	7 (5.1%)	16 (5.9%)
Black or African American	20 (14.8%)	20 (14.7%)	40 (14.8%)
White	65 (48.1%)	64 (47.1%)	129 (47.6%)
Multiple	11 (8.1%)	9 (6.6%)	20 (7.4%)
Unknown	4 (3.0%)	6 (4.4%)	10 (3.7%)
Not reported	1 (0.7%)	4 (2.9%)	5 (1.8%)
Race (stratification factor)			
n	135	136	271
Black	15 (11.1%)	17 (12.5%)	32 (11.8%)
Other	120 (88.9%)	119 (87.5%)	239 (88.2%)
Region (stratification factor)			
n	135	136	271
United States and Canada	20 (14.8%)	20 (14.7%)	40 (14.8%)
Latin America and the Caribbean	77 (57.0%)	77 (56.6%)	154 (56.8%)
Other	38 (28.1%)	39 (28.7%)	77 (28.4%)
Region (EU/non-EU)			
n	135	136	271
EU	27 (20.0%)	26 (19.1%)	53 (19.6%)
non-EU	108 (80.0%)	110 (80.9%)	218 (80.4%)
Weight (kg)			
n	135	136	271
Mean (SD)	66.26 (14.03)	68.29 (15.53)	67.28 (14.81)
Median	65.00	65.50	65.40
Min - Max	36.7 - 106.3	46.0 - 133.6	36.7 - 133.6

All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Table 20 Baseline disease characteristics (efficacy-evaluable patients)

	Obinutuzumab (N=135)	Placebo (N=136)	All Patients (N=271)
Serum Creatinine (umol/L)			
n	135	136	271
Mean (SD)	73.8 (34.1)	77.5 (42.2)	75.6 (38.4)
Median	70.0	65.0	68.0
Min - Max	30 - 332	24 - 388	24 - 388
eGFR (mL/min/1.73m2)			
n	135	136	271
Mean (SD)	102.8 (29.3)	101.9 (32.2)	102.3 (30.8)
Median	107.0	109.0	108.0
Min - Max	15 - 164	13 - 166	13 - 166
eGFR (mL/min/1.73m2) category			
n	135	136	271
<30	1 (0.7%)	1 (0.7%)	2 (0.7%)
30 - <60	12 (8.9%)	19 (14.0%)	31 (11.4%)
60 - <90	26 (19.3%)	20 (14.7%)	46 (17.0%)
>=90	96 (71.1%)	96 (70.6%)	192 (70.8%)
24-hour Urine Protein/Creatinine Ratio (mg/mg)			
n	134	136	270
Mean (SD)	3.14 (2.99)	3.53 (2.76)	3.34 (2.87)
Median	2.13	2.76	2.44
Min - Max	0.2 - 21.6	0.1 - 13.3	0.1 - 21.6
24-hour Urine Protein/Creatinine Ratio (mg/mg) category			
n	134	136	270
<3	82 (61.2%)	74 (54.4%)	156 (57.8%)
>=3	52 (38.8%)	62 (45.6%)	114 (42.2%)
anti-dsDNA category*			
n	135	136	271
Negative	78 (57.8%)	75 (55.1%)	153 (56.5%)
Positive	57 (42.2%)	61 (44.9%)	118 (43.5%)
C3 Complement (g/L) category			
n	135	136	271
<0.9	77 (57.0%)	76 (55.9%)	153 (56.5%)
>=0.9	58 (43.0%)	60 (44.1%)	118 (43.5%)
C4 Complement (g/L) category			
n	135	135	270
<0.1	32 (23.7%)	42 (31.1%)	74 (27.4%)
>=0.1	103 (76.3%)	93 (68.9%)	196 (72.6%)
Serum Albumin (g/L)			
n	135	136	271
Mean (SD)	34.7 (6.2)	34.0 (6.3)	34.4 (6.2)
Median	35.0	35.0	35.0
Min - Max	16 - 46	15 - 46	15 - 46
Baseline Lupus Nephritis (LN) class			
n	135	136	271
Class III	56 (41.5%)	51 (37.5%)	107 (39.5%)
Class IV	79 (58.5%)	85 (62.5%)	164 (60.5%)
Baseline LN concomitant class V			
n	135	136	271
Yes	47 (34.8%)	38 (27.9%)	85 (31.4%)
No	88 (65.2%)	98 (72.1%)	186 (68.6%)
Prior history of LN			
n	135	136	271
Yes	81 (60.0%)	76 (55.9%)	157 (57.9%)
No	54 (40.0%)	60 (44.1%)	114 (42.1%)

Duration of LN for patients who had prior history of LN (months)			
n	81	76	157
Mean (SD)	65.62 (78.64)	59.33 (64.70)	62.58 (72.07)
Median	36.60	34.30	36.50
Min - Max	0.4 - 330.4	0.8 - 217.8	0.4 - 330.4
Duration of LN calculated from time to biopsy for patients who did not have prior history of LN (months)			
n	54	60	114
Mean (SD)	1.61 (1.65)	1.38 (1.18)	1.49 (1.42)
Median	0.90	0.90	0.90
Min - Max	0.2 - 6.8	0.2 - 5.0	0.2 - 6.8
SLEDAI-2K			
n	135	133	268
Mean (SD)	12.1 (8.1)	12.4 (6.7)	12.2 (7.4)
Median	10.0	12.0	10.0
Min - Max	4 - 83	2 - 35	2 - 83

* Positive for anti-dsDNA is >120 kU/L. Negative for anti-dsDNA is <=120 kU/L.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Overall, 260 patients (97.0%) received at least one prior medication related to lupus nephritis before enrolling in the study, 135 (99.3%) in the obinutuzumab arm and 125 (94.7%) in the placebo arm. The most frequently reported prior medications related to lupus nephritis (i.e., in ≥10% of patients) were the following:

- Methylprednisolone: 159 patients (59.3%); 89 (65.4%) in the obinutuzumab arm vs. 70 (53.0%) in the placebo arm
- Anti-malarial agents: 109 patients (40.7%); 47 (34.6%) in the obinutuzumab arm vs. 62 (47.0%) in the placebo arm
- MMF: 108 patients (40.3%); 63 (46.3%) in the obinutuzumab arm vs. 45 (34.1%) in the placebo arm
- Other: prednisone: 83 patients (31.0%); 46 (33.8%) in the obinutuzumab arm vs. 37 (28.0%) in the placebo arm
- Azathioprine: 72 patients (26.9%); 40 (29.4%) in the obinutuzumab arm vs. 32 (24.2%) in the placebo arm
- Cyclophosphamide: 70 patients (26.1%); 41 (30.1%) in the obinutuzumab arm vs. 29 (22.0%) in the placebo arm.

A total of 10 patients (3.7%) received prior treatment with belimumab (4 [2.9%] in the obinutuzumab arm and 6 [4.5%] in the placebo arm) and 9 patients (3.4%) received prior treatment with rituximab (6 [4.4% in the obinutuzumab arm and 3 [2.3%] in the placebo arm).

The main classes of concomitant medication were the following:

- Immunosuppressants: 237 (88.4%); 120 (88.2%) in the obinutuzumab arm and 117 (88.6%) in the placebo arm
    - Azathioprine: 5 (1.9%); 4 (2.9%) in the obinutuzumab arm and 1 (0.8%) in the placebo arm
- Agents acting on the renin-angiotensin system: 236 (88.1%); 126 (92.6%) in the obinutuzumab arm and 110 (83.3%) in the placebo arm

- Lipid modifying agents: 76 (28.4%); 46 (33.8%) in the obinutuzumab arm and 30 (22.7%) in the placebo arm
- Antiprotozoals: 229 (85.4%); 115 (84.6%) in the obinutuzumab arm and 114 (86.4%) in the placebo arm.

Note that hydroxychloroquine (181 total patients [67.5%]) and hydroxychloroquine sulfate (39 total patients [14.6%]) are listed under both the immunosuppressant and antiprotozoal medication classes.

Numbers analysed

Table 21 Blinded Obinutuzumab exposure (safety-evaluable patients)

	Obinutuzumab (N=136)
Treatment duration (days)	
n	136
Mean (SD)	332.2 (99.1)
Median	365.0
Min - Max	1 - 415
Number of infusions	
n	136
Mean (SD)	5.1 (1.1)
Median	5.0
Min - Max	1 - 6
Number of infusions category	
n	136
1 dose	4 (2.9%)
2 doses	5 (3.7%)
3 doses	1 (0.7%)
4 doses	8 (5.9%)
5 doses	59 (43.4%)
6 doses	59 (43.4%)

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Includes data until the point of rescue for patients who received rescue therapy (except corticosteroid-only rescue). Includes the 76 weeks blinded treatment period.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Table 22 Mycophenolate mofetil exposure (safety-evaluable patients)

	Obinutuzumab (N=136)	Placebo (N=132)
Treatment duration (days)		
n	134	132
Mean (SD)	527.2 (96.3)	499.8 (128.6)
Median	558.0	558.0
Min - Max	59 - 562	24 - 562
Total cumulative dose (mg)		
n	134	132
Mean (SD)	1053371.64 (263458.33)	1072015.15 (317786.45)
Median	1099250.00	1113000.00
Min - Max	16000.0 - 1614500.0	40000.0 - 2310000.0

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.
Includes data until the point of rescue for patients who received rescue therapy (except corticosteroid-only rescue). Includes the 76 weeks blinded treatment period.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Table 23 Costricosteroids exposure (safety-evaluable patients)

	Obinutuzumab (N=136)	Placebo (N=132)
Treatment duration (days)		
n	136	132
Mean (SD)	519.4 (107.0)	494.3 (124.4)
Median	553.0	552.0
Min - Max	3 - 562	28 - 559
Total cumulative dose (mg)		
n	136	132
Mean (SD)	4628.17 (1652.57)	7319.97 (29905.91)
Median	4293.75	4366.25
Min - Max	120.0 - 12195.0	1415.0 - 347492.5

Treatment duration is the number of days on which patient received corticosteroids.
Premedication with methylprednisolone 80 mg IV were not included. Total dose represents prednisone equivalent dose.
Only corticosteroids administered PO, IV and IM are included.
Includes data until the point of rescue for patients who received rescue therapy (except corticosteroid-only rescue). Includes the 76 weeks blinded treatment period.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Outcomes and estimation

Primary endpoint

Table 24 Difference in Proportion of Patients in Complete Renal Response at Week 76, Efficacy-Evaluable Patients in REGENCY

	Obinutuzumab (N=135)	Placebo (N=136)
Observed Data		
n	131	135

Responders	60 (45.8%)	45 (33.3%)
Non-Responders	71 (54.2%)	90 (66.7%)
Main Analytical Approach (Multiple Imputations)		
Responders(%) (95% CI)	46.4 (37.95, 54.86)	33.1 (25.18, 41.00)
Adjusted Difference (95% CI)	13.40 (1.95, 24.84)	
p-value (Cochran-Mantel-Haenszel)	0.0232	

Complete renal response (CRR) is defined as achievement of all of the following:
- Urinary protein-to-creatinine ratio (UPCR) <0.5 g/g;
- Estimated glomerular filtration rate (eGFR) >=85% of baseline, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation;
- No occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal.

Patients experiencing the intercurrent event study treatment discontinuation were evaluated using their observed data under the treatment policy strategy.
Missing data was imputed by multiple imputations using fully conditional specification (FCS) predicted mean matching method.
Cochran-Mantel-Haenszel (CMH) test with stratification factors race and region was performed. The adjusted difference (i.e. common risk difference) and its CI based on stratified Newcombe CI were calculated using Mantel-Haenszel weights.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Table 25 Intercurrent events handled using composite strategy in the primary analysis, efficacy-evaluable patients

	Obinutuzumab (N=135)	Placebo (N=136)
Total number of patients with at least one intercurrent event	15 (11.1%)	34 (25.0%)
Treatment failure		
Total number of patients with at least one event	5 (3.7%)	24 (17.6%)
Chronic dialysis	0	1 (0.7%)
Clinically significant, sustained worsening in UPCR and/or eGFR from Week 24	5 (3.7%)	22 (16.2%)
ESRD	0	2 (1.5%)
Rescue therapy except corticosteroid-only rescue	4 (3.0%)	20 (14.7%)
Rescue therapy (including corticosteroid-only rescue)	8 (5.9%)	24 (17.6%)
Corticosteroid-only rescue	5 (3.7%)	11 (8.1%)
Death	3 (2.2%)	1 (0.7%)
Early study withdrawal		
Total number of patients with at least one event	9 (6.7%)	13 (9.6%)
Adverse event	0	1 (0.7%)
Death	3 (2.2%)	1 (0.7%)
Lost to follow-up	0	1 (0.7%)
Other	0	2 (1.5%)
Physician decision	0	3 (2.2%)
Withdrawal by subject	6 (4.4%)	5 (3.7%)

Complete renal response (CRR) is defined as achievement of all of the following:
- Urinary protein-to-creatinine ratio (UPCR) <0.5 g/g;
- Estimated glomerular filtration rate (eGFR) >=85% of baseline, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation;
- No occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal.

Patients experiencing the intercurrent event study treatment discontinuation were evaluated using their observed data under the treatment policy strategy.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Supplementary analyses

A supplementary analysis was performed where early study withdrawal was handled as missing data (provided the patient did not have any other intercurrent event resulting in the composite strategy being applied). The handling strategy for all other intercurrent events was the same as in the primary estimand. In total, 8 patients in the obinutuzumab arm and 6 patients in the placebo arm were handled as missing data. The proportion of patients who achieved CRR at Week 76 was greater in the obinutuzumab arm (47.7% [95% CI: 39.06, 56.26]) compared with the placebo arm (34.5% [95% CI: 26.41, 42.68]), with

an adjusted difference of 13.18% (95% CI: 1.47, 24.88; p-value = 0.0282). The number of patients with at least one intercurrent event of treatment failure, rescue therapy, or death (handled using the composite strategy) for this supplementary analysis was 11 patients (8.1%) in the obinutuzumab arm compared with 29 patients (21.3%) in the placebo arm.

Table 26 Supplementary analysis (treatment policy strategy): difference in proportion of patients in complete renal response at Week 76, efficacy-evaluable patients

	Obinutuzumab (N=135)	Placebo (N=136)
Observed Data		
n	125	122
Responders	61 (48.8%)	47 (38.5%)
Non-Responders	64 (51.2%)	75 (61.5%)
Main Analytical Approach (Multiple Imputations)		
Responders(%) (95% CI)	48.4 (39.81, 57.05)	36.0 (27.80, 44.29)
Adjusted Difference (95% CI)	12.68 (0.95, 24.42)	
p-value (Cochran-Mantel-Haenszel)	0.0352	

Complete renal response (CRR) is defined as achievement of all of the following:
- Urinary protein-to-creatinine ratio (UPCR) <0.5 g/g;
- Estimated glomerular filtration rate (eGFR) >=85% of baseline, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation;
- No occurrence of the following intercurrent event: death.

Patients experiencing the intercurrent events rescue therapy, treatment failure, or study treatment discontinuation were evaluated using their observed data under the treatment policy strategy. Patients who withdrew early from the study were considered as having missing data after their withdrawal.
Missing data was imputed by multiple imputations using fully conditional specification (FCS) predicted mean matching method.
Cochran-Mantel-Haenszel (CMH) test with stratification factors race and region was performed. The adjusted difference (i.e. common risk difference) and its CI based on stratified Newcombe CI were calculated using Mantel-Haenszel weights.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

A tipping point analysis, pre-specified in the SAP was performed to explore the plausibility of the missing data assumptions. The tipping point analysis targeted the estimand of the supplementary analysis based on the treatment policy strategy where all available data up to Week 76 were included and missing data were imputed by multiple imputations. However, for the tipping point analysis, instead of multiple imputations, single imputation was applied by setting patients in turn to a responder/non-responder status. In total, 10 patients in the obinutuzumab arm and 14 patients in the placebo arm had missing data. Results from the tipping point analysis showed if 2 additional obinutuzumab patients are assumed responders compared with placebo, it would result in the analysis being tipped to a statistically significant result (p-value < 0.05).

Table 27 Reasons why subjects did not reach CRR at Week 76, efficacy-evaluable patients

Outcome – CRR at Week 76	**Obinutuzumab (N = 135)**	**Placebo (N = 136)**
CRR, n (%)	**60 out of 131 (45.8%)**	**45 out of 135 (33.3%)**
Failure to reach CRR, n (%)	**71 out of 131 (54.2%)**	**90 out of 135 (66.7%)**
Reason for failure to reach CRR		
Not reaching CRR (either due to UPCR ≥ 0.5 or eGFR < 85% baseline)[a]	**56**	**56**
Experienced ICE	**15**	**34**

ICE – composite: Death	3	1
ICE - composite: Treatment failure due to new ESKD or need for chronic dialysis or renal transplantation	0	2
Observed Week 76 (Non-Responder)	0	0
Observed Week 76 (Responder)	0	0
Not observed at Week 76[b]	0	2
ICE - composite: Treatment failure due to clinically significant, sustained worsening from Week 24[c,d]	5	21
Observed Week 76 (Non-Responder)	3	14
Observed Week 76 (Responder)	0	2[e]
Not observed at Week 76[b]	2	5
ICE - composite: Receipt of rescue therapy (both as an ICE or as part of treatment failure ICE)	3	5
Observed Week 76 (Non-Responder)	2	4
Observed Week 76 (Responder)	1[f]	0
Not observed at Week 76[b]	0	1
ICE – composite: Early study withdrawal	4	5[g]
Additional Patients (Not reasons for failure to reach CRR)	**4**	**1**
Missing data - imputed by spot UPCR at Week 76	1	1
Missing data - imputed by multiple imputation	3	0

CRR = complete renal response, eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; ICE = intercurrent event; UPCR = urine protein-to-creatinine ratio

[a] Includes patients who did not have the intercurrent events of treatment failure, rescue therapy, death, early study withdrawal.

[b] Patients who dropped out of the study prior to Week 76 did not have observed data.

[c] Includes 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.

[d] 4 obinutuzumab patients and 17 placebo patients received rescue therapy through Week 76.

[e] 2 patients in the placebo arm with clinically significant worsening who were assessed as responders for the treatment policy analysis had received rescue therapy prior to Week 76 (one patient received tacrolimus and the other received belimumab and rituximab). Review of objective data from these patients is presented in REGENCY Primary CSR,

[f] 1 patient in the obinutuzumab arm that was assessed as a responder for the treatment policy analysis, received rescue therapy (oral corticosteroids) for management of a respiratory condition and administration was not related to lupus nephritis as per the investigator. Nonetheless, this obinutuzumab-treated patient was considered a treatment failure per protocol. Review of objective data from this patient is presented in REGENCY Primary CSR,

[g] Includes 3 patients in the placebo arm who did not receive any study treatment after randomization.

Table 28 Timing of intercurrent events up to Week 76, efficacy-evaluable patients

Type of ICE	Obinutuzumab (N=15)			Placebo (N=34)		
	Week ≤24	Week 24 to ≤50	Week 50 to ≤76	Week ≤24	Week 24 to ≤50	Week 50 to ≤76
Death	**2**	**0**	**1**	**0**	**1**	**0**
Treatment failure due to new ESKD or need for chronic dialysis or renal transplantation	**0**	**0**	**0**	**1**	**0**	**1**
Observed Week 76 (Non-Responder)	0	0	0	0	0	0
Observed Week 76 (Responder)	0	0	0	0	0	0
Not observed	0	0	0	1	0	1
Treatment failure due to clinically significant, sustained worsening from Week 24	**0**	**1**	**4**	**4**	**10**	**7**
Observed Week 76 (Non-Responder)	0	0	3	2	5	7
Observed Week 76 (Responder)	0	0	0	1	1	0
Not observed	0	1	1	1	4	0
Receipt of rescue therapy (both as an ICE or as part of treatment failure ICE)	**0**	**0**	**3**	**1**	**0**	**4**
Observed Week 76 (Non-Responder)	0	0	2	0	0	4
Observed Week 76 (Responder)	0	0	1	0	0	0
Not observed	0	0	0	1	0	0
Early study withdrawal (not observed)	**2**	**1**	**1**	**4[a]**	**0**	**1**
Total (any ICE)	**4**	**2**	**9**	**10**	**11**	**13**

ESKD = end-stage kidney disease; ICE = intercurrent event.

[a] Includes 3 patients in the placebo arm who did not receive any study treatment after randomization.

Secondary endpoints

Table 29 Key secondary endpoints

Endpoint	Obinutuzumab (N=135)	Placebo (N=136)
CRR with Successful Prednisone Taper at Week 76		
Responders (%) (95% CI)	42.7 (34.32, 51.09)	30.9 (23.12, 38.65)
Adjusted Difference in Proportions (%) (95% CI)	11.88 (0.57, 23.18)	
p-value	0.0421	
Proteinuric Response at Week 76		
Responders (%) (95% CI)	55.5 (47.09, 63.95)	41.9 (33.62, 50.20)
Adjusted Difference in Proportions (%) (95% CI)	13.68 (2.01, 25.36)	
p-value	0.0227[b]	

Mean Change in eGFR From Baseline to Week 76		
Adjusted Mean (SE)	2.31 (2.713)	−1.54 (2.706)
Difference in Adjusted Means (95% CI)	3.84 (−1.83, 9.51)	
p-value	0.1842	
Death or Renal Related Events Through Week 76		
Patients with events (%) (95% CI)	18.9 (12.11, 25.61)	35.6 (27.50, 43.78)
Adjusted Difference in Proportions (%) (95% CI)	−16.83 (−27.42, −6.23)	
p-value	0.0026[c]	
ORR at Week 50		
Responders (%) (95% CI)	59.1 (50.80, 67.43)	50.7 (42.16, 59.22)
Adjusted Difference in Proportions (%) (95% CI)	8.36 (−3.41, 20.12)	
p-value	0.1670	
Mean Change in FACIT-F Scale from Baseline to Week 76		
Adjusted Mean (SE)	1.76 (1.223)	3.11 (1.212)
Difference in Adjusted Means (95% CI)	−1.35 (−3.89, 1.20)	
p-value	0.2991	

CI = confidence interval; CRR = complete renal response; eGFR = estimated glomerular filtration rate; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; ORR = overall renal response; SE = standard error.

[a] To control the overall type I error, a fallback method maintaining a fixed sequence for testing was used (Section 3.7.1.2).

[b] Statistical significance test was performed at 4% level of significance to account for multiplicity (Section 3.7.1.2).

[c] Even though the p-value = 0.0026, statistical significance cannot be claimed as the earlier key secondary endpoint in the hierarchy was not met.

Note: Missing data was handled using multiple imputation methods.

Supportive secondary endpoints

Supportive secondary endpoints were not type 1 error-controlled.
The adjusted mean change in log anti-dsDNA titers from baseline to Week 50 was greater in the obinutuzumab arm (−0.38 [SE: 0.100]) compared with the placebo arm (−0.01 [SE: 0.099]), with a difference in adjusted means of −0.36 (95% CI: 0.57, 0.16; nominal p-value = 0.0006).

The adjusted mean change in C3 from baseline to Week 50 was 0.20 g/L (SE: 0.030) in the obinutuzumab arm and 0.06 g/L (SE: 0.030) in the placebo arm, with a difference in adjusted means of 0.14 g/L (95% CI: 0.08, 0.20; nominal p-value < 0.0001).

The adjusted mean change in SLEDAI-2K from baseline to Week 76 was similar in the obinutuzumab arm (−5.63 [SE: 1.456]) compared with the placebo arm (−5.51 [SE: 1.432]), with a difference in adjusted means of −0.12 (95% CI: −3.11, 2.87; nominal p-value=0.9384).

Table 30 Time to onset of complete renal response over the course of 76 weeks, efficacy-evaluable patients

	Obinutuzumab (N=135)	Placebo (N=136)
Patients with event (%)	70 (51.9%)	55 (40.4%)
Patients without event (%)	65 (48.1%)	81 (59.6%)
Time to event (weeks)		
Median	76.4	80.3
95% CI	(76.1, 77.4)	(76.3, NE)
25% and 75%-ile	49.9 - 79.7	50.1 - 80.3
Range	24 - 80	24 - 80
Stratified Analysis		
p-value (log-rank)	0.1324	
Hazard Ratio	1.31	
95% CI	(0.91, 1.89)	

* censored observation. NE = Not Estimable.
Complete renal response (CRR) is defined as achievement of all of the following:
- Urinary protein-to-creatinine ratio (UPCR) <0.5 g/g;
- Estimated glomerular filtration rate (eGFR) >=85% of baseline, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation;
- No occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal.
Patients who experienced rescue therapy, treatment failure, death, or early study withdrawal before achieving CRR were censored at Week 76. Patients who completed the 76-week treatment period and did not experience CRR were censored at Week 76.
Summary statistics of time to onset of CRR (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 of race and region.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Other efficacy endpoints

The exploratory endpoints presented in this section were not type I error–controlled.

The proportion of patients who achieved the individual components of CRR at Week 76 was numerically higher in the obinutuzumab arm compared with the placebo arm for all three components:

- UPCR $<$ 0.5 g/g (Obinutuzumab: 47.4% vs. Placebo: 36.0%)
- eGFR $\geq$ 85% of baseline (Obinutuzumab: 83.7% vs. Placebo: 75.7%)
- No occurrence of intercurrent events (Obinutuzumab: 88.9% vs. Placebo: 75.0%)

Table 31 eGFR slope from Week 12 to Week 76, efficacy-evaluable patients

	Obinutuzumab (N=135)	Placebo (N=136)
eGFR (mL/min/1.73m2/year)		
Estimated eGFR Slope (SE)	-0.71 (1.452)	-4.39 (1.454)
95% CI for eGFR Slope	(-3.55, 2.14)	(-7.24, -1.54)
Difference in eGFR Slope (SE)	3.68 (2.055)	
95% CI for Difference in eGFR Slope	(-0.35, 7.72)	
p-value	0.0732	

The eGFR slope was analyzed using a mixed effect model with random intercept and random slope.
The difference in eGFR slope shows annualized difference.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Table 32 Change in UPCR from baseline by Visit, efficacy-evaluable patients

Visit	Obinutuzumab (N=135)	Placebo (N=136)
Week 24		
n	123	126
Mean (SD)	-1.51 (2.47)	-1.58 (2.21)
Median	-1.08	-1.28
Min - Max	-18.4 - 3.0	-11.6 - 3.4
Week 50		
n	122	114
Mean (SD)	-1.70 (2.88)	-1.73 (2.71)
Median	-1.43	-1.31
Min - Max	-19.1 - 8.0	-12.1 - 7.9
Week 76		
n	120	118
Mean (SD)	-1.89 (2.92)	-1.68 (2.79)
Median	-1.53	-1.47
Min - Max	-21.1 - 5.8	-12.8 - 12.1

UPCR = 24-hour urinary protein-to-creatinine ratio.
Includes only observed laboratory values through 76 weeks blinded treatment period.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Table 33 Time to LN fare from Week 24 through Week 76, efficacy-evaluable patients

	Obinutuzumab (N=135)	Placebo (N=136)
Patients with event (%)	15 (11.1%)	32 (23.5%)
Patients without event (%)	120 (88.9%)	104 (76.5%)
Time to event (weeks)		
Median	NE	NE
95% CI	NE	NE
25% and 75%-ile	NE	79.6 - NE
Range	1* - 81*	0* - 80*
Stratified Analysis		
p-value (log-rank)	0.0074	
Hazard Ratio	0.44	
95% CI	(0.24, 0.82)	

* censored observation. NE = Not Estimable.
LN flare from Week 24, 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; or
- Receipt of rescue therapy, except for corticosteroid-only rescue.
Patients who experienced early study withdrawal before experiencing the event were censored at the time of the study withdrawal. Patients who completed the 76-week treatment period and did not experience the event were censored at the upper limit of the Week 76 visit window.
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.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Obinutuzumab regimens 2-2-1 vs 2-2-2

Table 34 Difference in proportion of patients in complete renal response at Week 76 by obinutuzumab dose regimen, efficacy-evaluable patients

	Obinutuzumab Arm 1 (2-2-2 Regimen) (N=69)	Obinutuzumab Arm 2 (2-2-1 Regimen) (N=66)	Placebo (N=136)
Observed Data			
n	66	65	135
Responders	31 (47.0%)	29 (44.6%)	45 (33.3%)
Non-Responders	35 (53.0%)	36 (55.4%)	90 (66.7%)
Main Analytical Approach (Multiple Imputations)			
Responders(%) (95% CI)	46.9 (35.02, 58.83)	45.5 (33.44, 57.47)	33.1 (25.18, 41.00)
Adjusted Difference (95% CI)	13.95 (-0.06, 27.96)	12.67 (-1.49, 26.72)	

Complete renal response (CRR) is defined as achievement of all of the following:
- Urinary protein-to-creatinine ratio (UPCR) <0.5 g/g;
- Estimated glomerular filtration rate (eGFR) >=85% of baseline, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation;
- No occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal.
Patients experiencing the intercurrent event study treatment discontinuation were evaluated using their observed data under the treatment policy strategy.
Missing data was imputed by multiple imputations using fully conditional specification (FCS) predicted mean matching method.
The adjusted difference (i.e. common risk difference) and its CI based on stratified Newcombe CI were calculated using Mantel-Haenszel weights. Adjusted difference row shows the adjusted difference between obinutuzumab arm 1 and placebo, and the adjusted difference between obinutuzumab arm 2 and placebo.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Blinded obinutuzumab treatment beyond Week 76

Table 35 **Difference in Proportion of Patients in Complete Renal Response by Visit in Blinded Treatment After Week 76 Period Using Previous Visit Imputation Strategy, Post Week 76 Blinded Treatment Efficacy-Evaluable Patients in REGENCY**

Difference in Proportion of Patients in Complete Renal Response by Visit in Blinded Treatment After Week 76 Period Using Previous Visit Imputation Strategy, Post Week 76 Blinded Treatment Efficacy-Evaluable Patients
Protocol: CA41705

Visit	Obinutuzumab (N=74)	Placebo (N=60)
Week 76		
n	74	60
Responders	51 (68.9%)	41 (68.3%)
95% CI	(57.66, 78.31)	(55.77, 78.69)
Adjusted Difference (95% CI)	1.19 (-14.31, 17.08)	
Blinded Treatment Week 106		
n	72	58
Responders	48 (66.7%)	38 (65.5%)
95% CI	(55.18, 76.47)	(52.67, 76.44)
Adjusted Difference (95% CI)	2.46 (-13.66, 18.79)	
Blinded Treatment Week 132		
n	58	49
Responders	42 (72.4%)	28 (57.1%)
95% CI	(59.80, 82.25)	(43.27, 69.98)
Adjusted Difference (95% CI)	16.48 (-1.89, 33.66)	
Blinded Treatment Week 158		
n	47	42
Responders	33 (70.2%)	23 (54.8%)
95% CI	(56.02, 81.35)	(39.95, 68.78)
Adjusted Difference (95% CI)	15.14 (-4.91, 33.95)	
Blinded Treatment Week 184		
n	29	33
Responders	19 (65.5%)	21 (63.6%)
95% CI	(47.35, 80.06)	(46.62, 77.81)
Adjusted Difference (95% CI)	0.81 (-22.79, 24.18)	
Blinded Treatment Week 210		
n	18	12
Responders	12 (66.7%)	3 (25.0%)
95% CI	(43.75, 83.72)	(8.89, 53.23)
Adjusted Difference (95% CI)	37.44 (-0.06, 62.71)	

Complete renal response (CRR) is defined as achievement of all of the following:
- UPCR <0.5 g/g;
- eGFR >=85% of baseline, as calculated using the CKD-EPI equation;
- No occurrence of the following intercurrent events: rescue therapy, treatment failure, death, early study withdrawal or entering into the OLT.

Patients experiencing the intercurrent event study treatment discontinuation were evaluated using their observed data under the treatment policy strategy. Intercurrent event entering into SFU was handled using a hypothetical strategy targeting an effect that would occur in the hypothetical scenario in which no patient entered into SFU. Data after patients entered into SFU were imputed. Previous visit imputation strategy, where a measurement can only be carried forward to the next response assessment, but not beyond that, was used to impute the missing data. Missing Week 106 data was imputed from either Week 80 or Week 76, as patients who moved to study follow up period did not have scheduled Week 80 assessments. Missing 24-hour UPCR was imputed using spot UPCR from the same visit, followed by 24-hour and spot UPCR from the previous visit. Patients with missing measurements after this imputation strategy were set to non-responders. The adjusted difference (i.e. common risk difference) and its CI based on stratified Newcombe CI were calculated using Mantel-Haenszel weights.

All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Table 36 Difference in Proportion of Patients in Complete Renal Response by Visit in Blinded Treatment After Week 76 Period Using Previous Visit Imputation Strategy, Efficacy-Evaluable Patients in REGENCY

Difference in Proportion of Patients in Complete Renal Response by Visit in Blinded Treatment After Week 76 Period Using Previous Visit Imputation Strategy, Efficacy-Evaluable Patients
Protocol: CA41705

Visit	Obinutuzumab (N=135)	Placebo (N=136)

Week 76		
n	135	136
Responders	62 (45.9%)	45 (33.1%)
95% CI	(37.75, 54.33)	(25.74, 41.37)
Adjusted Difference (95% CI)	12.92 (1.28, 24.09)	
Blinded Treatment Week 106		
n	130	133
Responders	54 (41.5%)	42 (31.6%)
95% CI	(33.43, 50.13)	(24.29, 39.90)
Adjusted Difference (95% CI)	9.95 (-1.67, 21.23)	
Blinded Treatment Week 132		
n	104	105
Responders	42 (40.4%)	28 (26.7%)
95% CI	(31.46, 49.99)	(19.14, 35.84)
Adjusted Difference (95% CI)	13.86 (1.05, 26.11)	
Blinded Treatment Week 158		
n	85	85
Responders	33 (38.8%)	23 (27.1%)
95% CI	(29.16, 49.45)	(18.76, 37.34)
Adjusted Difference (95% CI)	10.76 (-3.54, 24.44)	
Blinded Treatment Week 184		
n	60	61
Responders	19 (31.7%)	21 (34.4%)
95% CI	(21.31, 44.23)	(23.75, 46.95)
Adjusted Difference (95% CI)	-1.79 (-18.12, 14.69)	
Blinded Treatment Week 210		
n	32	28
Responders	12 (37.5%)	3 (10.7%)
95% CI	(22.93, 54.75)	(3.71, 27.20)
Adjusted Difference (95% CI)	26.73 (3.58, 45.40	

Complete renal response (CRR) is defined as achievement of all of the following:
- UPCR <0.5 g/g;
- eGFR >=85% of baseline, as calculated using the CKD-EPI equation;
- No occurrence of the following intercurrent events: rescue therapy, treatment failure, death, early study withdrawal or entering into the OLT.

Patients experiencing the intercurrent event study treatment discontinuation were evaluated using their observed data under the treatment policy strategy. Intercurrent event entering into SFU was handled using a hypothetical strategy targeting an effect that would occur in the hypothetical scenario in which no patient entered into SFU. Data after patients entered into SFU were imputed. Previous visit imputation strategy, where a measurement can only be carried forward to the next response assessment, but not beyond that, was used to impute the missing data. Missing Week 106 data was imputed from either Week 80 or Week 76, as patients who moved to study follow up period did not have scheduled Week 80 assessments. Missing 24-hour UPCR was imputed using spot UPCR from the same visit, followed by 24-hour and spot UPCR from the previous visit. Patients with missing measurements after this imputation strategy were set to non-responders. The adjusted difference (i.e. common risk difference) and its CI based on stratified Newcombe CI were calculated using Mantel-Haenszel weights.

All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.

Summary of main study(ies)

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37 ***Summary of Efficacy for REGENCY trial***

Title: Study CA41705 (REGENCY)—A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Obinutuzumab in Patients with ISN/RPS 2003 Class III or IV Lupus Nephritis.

Study identifier	CA41705	
Design	Phase III, multicentre, double-blind, randomized, parallel-group, placebo-controlled intervention	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	76 Weeks Not applicable The end of REGENCY is defined as the date when the last patient, last visit occurs or the date at which SFU is received from the last patient up to a maximum of 18 months from the last obinutuzumab infusion (blinded and open-label). The end of study is expected to occur approximately 5 years after the last patient is enrolled.
Hypothesis	Superiority	
Intervention groups	Obinutuzumab	2-2-2 regimen: Day 1 and Week 2, 24+26 and 50+52, randomized n=66 2-2-1 regimen: Day 1 and Week 2, 24+26 and 52, placebo at Week 50, randomized n=69 In total randomized in obinutuzumab arm: n=135
	Placebo	Day 1 and Week 2, 24+26 and 50+52, randomized n=136
Endpoints and definitions	Primary endpoint: CRR at Week 76	Proportion of patients who achieved a CRR at Week 76, with CRR defined as achievement of all of the following: - 24-hour UPCR < 0.5 g/g - 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
	Secondary key endpoint: CRR with successful prednisone taper at Week 76	Achievement of CRR (as defined above) at Week 76 with no receipt of prednisone > 7.5 mg/day (or equivalent) from Week 64 through Week 76
	Secondary key endpoint: Proteinuric response at Week 76	Proteinuric response 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
	Secondary key endpoint: Mean change in eGFR from baseline to Week 76	eGFR calculated using the CKD-EPI equation

	Secondary key endpoint: Death or renal related events through Week 76	Death or renal-related events were the following: - Death - Treatment failure, defined as present if any of the following criteria were met: - New end-stage renal disease - Need for chronic dialysis - Renal transplantation - Clinically significant, sustained worsening in UPCR and/or eGFR from Week 24 onward that leads the investigator to conclude the patient failed the randomized treatment regimen - Receipt of rescue therapy, except for corticosteroid-only rescue - Worsening proteinuria, defined as a confirmed ≥ 50% increase in UPCR to a value ≥ 3 - Worsening eGFR, defined as a confirmed ≥ 30% decrease in eGFR to a value < 60
	Secondary key endpoint: ORR at Week 50	Achievement of ORR was defined as either CRR or PRR evaluated at Week 50. PRR was defined as achievement of all of the following: - ≥ 50% reduction in UPCR from baseline - UPCR < 1 (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
	Secondary key endpoint: Change in FACIT-F scale from baseline to Week 76	The FACIT–F Scale is a patient-completed questionnaire consisting of 13 items that assess fatigue and has been validated in patients. Instrument scoring yields a range from 0 to 52, with higher scores representing better patient status (less fatigue).
Data cutoff date	15AUG2024	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy-evaluable population: All randomized patients regardless of whether they received study treatment (obinutuzumab or placebo).		
Descriptive statistics and estimate variability	Intervention groups	Obinutuzumab	Placebo
	Number of subjects	N = 131[d]	N = 135[d]
Primary endpoint: CRR at Week 76			
Effect estimate per comparison	Responders (%) (95% CI)[d]	46.4 (37.95, 54.86)	33.1 (25.18, 41.00)
	Adjusted Difference in Proportions (%) (95% CI)	13.40 (1.95, 24.84)	
	Two-sided p-value	0.0232	
Secondary key endpoint[a]: CRR with successful prednisone taper at Week 76			
Effect estimate per comparison	Responders (%) (95% CI)[d]	42.7 (34.32, 51.09)	30.9 (23.12, 38.65)
	Adjusted Difference in Proportions (%) (95% CI)	11.88 (0.57, 23.18)	
	Two-sided p-value	0.0421	

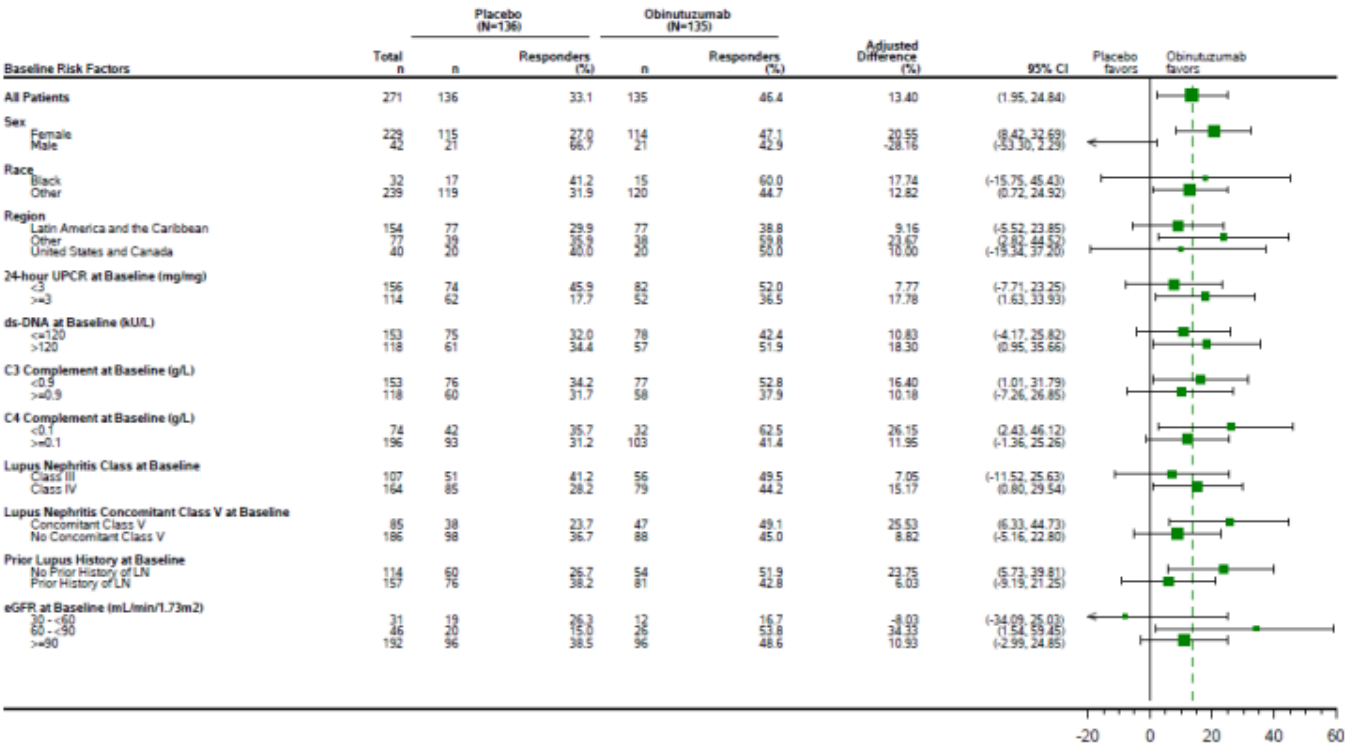
Secondary key endpoint[a]: Proteinuric Response at Week 76			
Effect estimate per comparison	Responders (%) (95% CI)[d]	55.5 (47.09, 63.95)	41.9 (33.62, 50.20)
	Adjusted Difference in Proportions (%) (95% CI)	13.68 (2.01, 25.36)	
	Two-sided p-value	0.0227[b]	
Secondary key endpoint[a]: Mean Change in eGFR From Baseline to Week 76			
Effect estimate per comparison	Responders (%) (95% CI)[d]	2.31 (2.713)	− 1.54 (2.706)
	Adjusted Difference in Proportions (%) (95% CI)	3.84 (− 1.83, 9.51)	
	Two-sided p-value	0.1842	
Secondary key endpoint[a]: Death or Renal Related Events Through Week 76			
Effect estimate per comparison	Responders (%) (95% CI)[d]	18.9 (12.11, 25.61)	35.6 (27.50, 43.78)
	Adjusted Difference in Proportions (%) (95% CI)	− 16.83 (− 27.42, − 6.23)	
	Two-sided p-value	0.0026[c]	
Secondary key endpoint[a]: ORR at Week 50			
Effect estimate per comparison	Responders (%) (95% CI)[d]	59.1 (50.80, 67.43)	50.7 (42.16, 59.22)
	Adjusted Difference in Proportions (%) (95% CI)	8.36 (− 3.41, 20.12)	
	Two-sided p-value	0.1670	
Secondary key endpoint[a]: Mean Change in FACIT-F Scale from Baseline to Week 76			
Effect estimate per comparison	Responders (%) (95% CI)[d]	1.76 (1.223)	3.11 (1.212)
	Adjusted Difference in Proportions (%) (95% CI)	− 1.35 (− 3.89, 1.20)	
	Two-sided p-value	0.2991	
Notes	a To control the overall type I error, a fallback method maintaining a fixed sequence for testing was used. b Statistical significance test was performed at 4% level of significance to account for multiplicity. c Even though the p-value =0.0026, statistical significance cannot be claimed as the earlier key secondary endpoint in the hierarchy was not met. d The denominators of n=131 (Gazyvaro) and n=135 (placebo) used in analyses of both the primary and secondary key endpoints do not match with the number of patients in the Efficacy-evaluable population (n=135 (Gazyvaro) and n=136 (placebo)). The MAH has been asked to explain this discrepancy and provide sensitivity analyses using the observed response rate.		

Ancillary analyses

N/A

Clinical studies in special populations

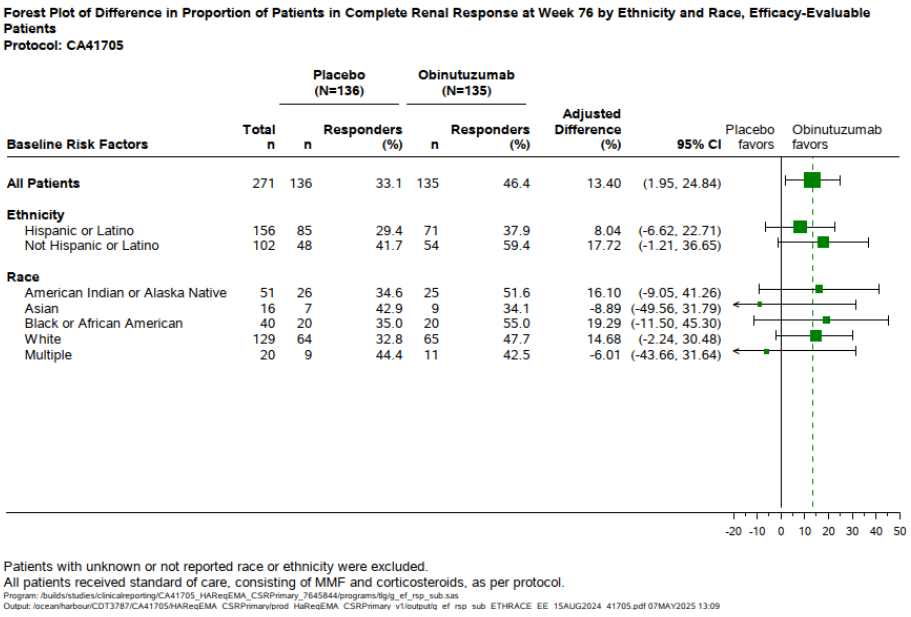
Figure 29 Forest plot of difference in proportion of patients in complete renal response at Week 76 by subgroup, efficacy-evaluable patients



Anti-ds-DNA= anti-double stranded DNA antibodies; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; MMF= mycophenolate mofetil; UPCR = urine protein creatinine ratio

Upon the CHMP's request, the MAH provided the following post hoc subgroup analyses of CRR:

Figure 30 Forest Plot of Difference in Proportion of Patients in Complete Renal Response at Week 76 by Ethnicity and Race Subgroups, Efficacy-Evaluable Patients in REGENCY



Patients with unknown or not reported race or ethnicity were excluded.
All patients received standard of care, consisting of MMF and corticosteroids, as per protocol.
Program: /builds/studies/clinicalreporting/CA41705_HAReqEMA_CSRPrimary_7645844/programs/tlg/g_ef_rsp_sub.sas
Output: /ocean/harbour/CDT3787/CA41705/HAReqEMA_CSRPrimary/prod_HaReqEMA_CSRPrimary_v1/output/g_ef_rsp_sub_ETHRACE_EE_15AUG2024_41705.pdf 07MAY2025 13:09

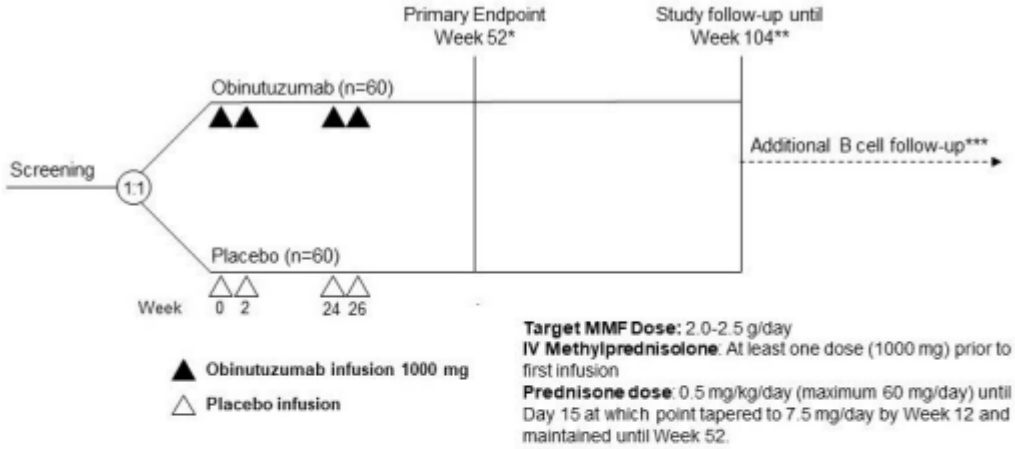
Supportive study(ies)

Supportive Study: NOBILITY (WA29748)

Methods

NOBILITY was a Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter study that evaluated the safety and efficacy of obinutuzumab in patients with ISN/RPS 2003 Class III or IV lupus nephritis, with or without concomitant Class V, treated with SoC therapy consisting of MMF/MPA and corticosteroids.

Figure 31 Nobility study schema



MMF = mycophenolate mofetil.

Notes:

1. Per protocol, mycophenolic acid at equivalent doses of 1440–1800 mg/day could be substituted for MMF at investigator discretion.
2. The sample sizes shown are the planned patient recruitment numbers.

* After Week 52, background immunosuppression adjusted at investigator discretion.

** Patients and investigators remained blinded until Week 104.

*** Additional B cell follow-up (BCFU) visits occurred until patients achieved either their baseline CD19-positive count or 25 cells/μL (the lower limit of normal of CD19-positive B cells for this lupus population) or BCFU visits for all patients ended, whichever occurred first.

After Week 52, patients entered the follow-up during which they received SoC treatment per the investigator's best medical judgment. The investigators continued to be blinded to the treatment allocation during the follow-up period. Follow-up visits were scheduled at Weeks 76 and 104. Patients who did not achieve their baseline CD19-positive B cell count or 25 cells/μL CD19-positive count (LLN for this lupus population under study) entered additional B-cell follow-up (BCFU) after Week 104. Additional visits occurred every 6 months until patients achieved either their baseline CD19-positive count or achieved 25 cells/μL CD19-positive count, whichever occurred first. The study has been completed with last patient last visit (LPLV) on 2 August 2023 when BCFU visits for all patients ended.

Study participants

The key eligibility criteria for Nobility study are included in *Table 9*.

Treatments

Blinded Treatment (Up to Week 52 Visit)

After screening, eligible patients were randomized in a 1:1 ratio to receive either obinutuzumab 1000 mg (administered as an absolute [flat] dose by IV infusion on Days 1, 15, 168, and 182) or placebo (infused in the same volume and on the same scheduled days as active treatment).

Prior to each study treatment infusion, patients randomized to obinutuzumab received 80 mg methylprednisone IV and patients randomized to placebo received methylprednisone placebo; all patients received acetaminophen (650-1000 mg) PO and diphenhydramine 50 mg PO (or equivalent dose of a similar agent).

In addition to obinutuzumab or placebo, all patients received antihypertensive therapy, antimalarial therapy, MMF, and corticosteroids (see Table 4). Patients in both treatment arms continued or initiated either MMF or MPA during screening or no later than Day 1. MMF or MPA were given in two or three divided doses and titrated by Week 4 to 2.0-2.5 g/day for MMF or 1440-1800 mg/day for MPA. Oral corticosteroids were initiated at a dose of 0.5 mg/kg (maximum 60 mg/day) and were tapered over 10 weeks to a total daily maintenance dose of 7.5 mg/day by Week 12 and maintained at this dose until Week 52 (i.e., the primary endpoint assessment). Patients received methylprednisolone 1000 mg IV prior to or during screening and were permitted to receive up to a total of 3000 mg methylprednisolone IV prior to randomization for severe clinical activity according to guidelines of routine care for these patients.

The randomization of patients into active treatment or placebo was performed according to a stratified permuted block design, stratified by race (Afro-Caribbean/African American vs. Other) and region (United States vs. non-United States).

No further doses of study treatment were administered after Week 26. The primary efficacy endpoint was assessed at Week 52.

Beyond Week 52 Visit (Follow-up)

After Week 52, patients entered the follow up during which they received SoC treatment per the investigator's best medical judgment. The investigators continued to be blinded to the treatment allocation during the follow-up period. Follow up visits were scheduled at Weeks 76 and 104.

Patients who did not achieve their baseline CD19-positive B cell count or 25 cells/μL CD19-positive count (LLN for this lupus population under study) entered additional B-cell follow-up (BCFU) after Week 104. Additional visits occurred every 6 months until patients achieved either their baseline CD19-positive count or achieved 25 cells/μL CD19-positive count, whichever occurred first.

Premedications to Reduce the Risk of Infusion-Related Reactions (IRR) in in Nobility study are provided in Table 10. Standard therapies in Nobility study are provided in Table 11.

Objectives and Endpoints

Table 38 Objectives and corresponding endpoints for Nobility study

Objectives	Corresponding Endpoints
Primary Efficacy Objective	**Corresponding Primary Efficacy Endpoints**

• To assess the ability of obinutuzumab compared with placebo to achieve a CRR at Week 52, as assessed by improvements in renal function, urinary sediment, and proteinuria in patients with active ISN/RPS Class III or IV LN.	Proportion of patients who achieved a CRR, evaluated at Week 52.
	CRR was defined as achievement of all of the following:
	• Normalization of serum creatinine as evidenced by the following:
	  • Serum creatinine ≤the ULN range of central laboratory values if the baseline (Day 1) serum creatinine is above the ULN
	  • Serum creatinine ≤15% above baseline and ≤the ULN range of central laboratory values if baseline (Day 1) serum creatinine is ≤the ULN range of central laboratory values
	• Inactive urinary sediment, as evidenced by <10 red blood cells/high power field and the absence of red cell casts
	• Urinary protein to creatinine ratio (UPCR) <0.5

Secondary Efficacy Objective	**Corresponding Secondary Efficacy Endpoints [a]**

• Assess overall renal response (CRR or PRR) [b]
• Evaluate the ability of obinutuzumab to improve time to response (CRR or PRR) [b] over the course of 52 weeks
	• Proportion of patients who achieve an overall renal response at Week 52 (CRR or PRR)
	• Proportion of patients who achieve a modified CRR (mCRR1) at Week 52 as defined by the normalization of serum creatinine as evidenced by the following:
	  • Serum creatinine ≤ the ULN range of central laboratory values if baseline (Day 1) serum creatinine is above the ULN
	  • Serum creatinine ≤ 15% above baseline and ≤ the ULN range of central laboratory values if baseline (Day 1) serum creatinine ≤ the ULN range of central laboratory values
	  • UPCR < 0.5
	• Proportion of patients who achieve a second modified CRR (mCRR2) at Week 52
	  • Serum creatinine ≤ 15% above baseline if baseline (Day 1) serum creatinine is above the normal range of the central laboratory values
	  • Serum creatinine ≤ 15% above baseline and ≤ the ULN range of central laboratory values if baseline (Day 1) serum creatinine ≤ the ULN range of central laboratory values
	  • Inactive urinary sediment (as evidenced by < 10 red blood cells/high power field (RBCs/HPF) and the absence of red cell casts)
	  • UPCR < 0.5
	• Proportion of patients who achieve a third modified CRR (mCRR3) at Week 52 as defined by attainment of serum creatinine ≤ ULN range of central laboratory values and urinary protein to creatinine ratio of < 0.5
	• Time to CRR, over the course of 52 weeks
	• Time to overall renal response (CRR or PRR) over the course of 52 weeks
	• Change in anti-double stranded deoxyribonucleic acid (dsDNA) titer, C3 and C4 from baseline at Week 52
	• Proportion of patients who achieve a PRR at Week 52
	• Proportion of patients who achieve a CRR at Week 24

Sample size calculations

This Phase II study is a proof-of-concept study that was designed to detect an improvement in CRR. The primary efficacy endpoint of this study was the proportion of patients that achieve CRR. It was estimated that approximately 30% of patients with proliferative LN who are receiving MMF (or equivalent) will achieve a CRR at Week 52 and that the addition of obinutuzumab to MMF (or equivalent) would induce an overall CRR rate of 50% at Week 52. On the basis of these assumptions, a total of 120 patients randomized to obinutuzumab- and placebo-treated groups in a 1:1 ratio (60 patients in each of the obinutuzumab- and placebo-treated groups) would yield approximately 83% power at the two-sided α= 0.2 significance level using a Cochrane-Mantel-Haenzel (CMH) test, assuming the same CRR proportions across the strata.

Statistical analyses

Primary endpoint: The proportions of patients achieving CRR across treatment groups were compared using a CMH test with race (Afro-Caribbean/African American versus others) and region (United States versus non-United States) as stratification factors. If the test resulted in favour of the obinutuzumab

group at $\alpha <$ 0.1-level (one-sided), it would be concluded that there is a shift toward better renal response associated with the obinutuzumab group.

Secondary endpoints: The proportion of patients who achieve an overall response at Week 52 (CRR+PRR) were analyzed using a CMH test, with race and region as strata. Time to first overall response (CRR+PRR) over the course of 52 weeks were presented using Kaplan-Meier methodology and compared between treatment groups using a stratified log-rank test with race and region as strata. Time to CRR during this period was analyzed similarly. The percent change from baseline and mean and median assessments of biomarkers of LN disease activity were analyzed using appropriate statistical methodology. The proportions of patients who achieve a CRR at Week 24 were analyzed using the same methodology as the primary analysis. In addition, the modified definitions, mCRR1, mCRR2, and mCRR3, of CRR were analyzed in this way to assess the sensitivity of CRR to its definition. Sensitivity analyses were performed to assess the potential impact on the primary endpoint, and possibly also key secondary endpoints, of missing data and possibly also changes to background immunosuppressive medication.

Changes following Study Unblinding/Database Lock

The following changes were made compared to the planned analyses in SAP v2:

- SAP v2, Section 4.1 Analysis Populations: two additional analyses populations are presented in this report compared to those planned in SAP v2:
    - The B cell depleted population includes patients with CD19-positive B cell below the lower limit of quantification (LLOQ) after receiving treatment at any time during the study treatment period.
    - B Cell Follow-up population includes patients who did not achieve their baseline CD19-positive B cell count or lower limit of normal (LLN) of the lupus population and entered the additional BCFU after Week 104.
- SAP v2, Section 4.6 Efficacy Analysis: the list of endpoints in SAP v2 is specific to the primary timepoint, i.e. at Week 52. However, because the Sponsor planned to report all available study data in the final locked database, this report also presents post-week 52 results (notably, data at Week 76 and/or Week 104 timepoints) to present additional efficacy results.

Results

Table 39 Patient disposition (all randomized patients)

	Obi + MMF (N=64)	Placebo + MMF (N=62)	All (N=126)
Signed Informed Consent	64 (100.0%)	62 (100.0%)	126 (100.0%)
Randomized	64 (100.0%)	62 (100.0%)	126 (100.0%)
Treated	63 (98.4%)	62 (100.0%)	125 (99.2%)
Completed Planned Treatment	59 (92.2%)	58 (93.5%)	117 (92.9%)
Entered BCFU Period	17 (26.6%)	6 (9.7%)	23 (18.3%)
Discontinued Planned Treatment	5 (7.8%)	4 (6.5%)	9 (7.1%)
Death	0	2 (3.2%)	2 (1.6%)
Lack Of Efficacy	1 (1.6%)	0	1 (0.8%)
Pregnancy	2 (3.1%)	0	2 (1.6%)
Withdrawal By Subject	2 (3.1%)	2 (3.2%)	4 (3.2%)
Completed Study	55 (85.9%)	44 (71.0%)	99 (78.6%)
Discontinued Study	9 (14.1%)	18 (29.0%)	27 (21.4%)
Pregnancy	1 (1.6%)	0	1 (0.8%)
Death	1 (1.6%)	4 (6.5%)	5 (4.0%)
Lack Of Efficacy	1 (1.6%)	0	1 (0.8%)
Lost To Follow-Up	1 (1.6%)	3 (4.8%)	4 (3.2%)
Withdrawal By Subject	4 (6.3%)	7 (11.3%)	11 (8.7%)
Physician Decision	0	2 (3.2%)	2 (1.6%)
Receipt Of Additional Therapies That Reduce Peripheral B-Cell Counts	0	2 (3.2%)	2 (1.6%)
Post Trial Access	1 (1.6%)	0	1 (0.8%)

Obi = Obinutuzumab; MMF = Mycophenolate Mofetil.
BCFU: extended B-cell follow-up period.
Percentages are based on N.

Table 40 Demographic and baseline characteristics (mITT population)

	Obi + MMF (N=63)	Placebo + MMF (N=62)	All (N=125)
Gender			
n	63	62	125
Male	8 (12.7%)	11 (17.7%)	19 (15.2%)
Female	55 (87.3%)	51 (82.3%)	106 (84.8%)
Age (years)			
n	63	62	125
Mean (SD)	33.1 (9.84)	31.9 (10.07)	32.5 (9.93)
Median	32.0	30.0	31.0
Q1 - Q3	24.0 - 40.0	24.0 - 39.0	24.0 - 40.0
Min - Max	18 - 59	18 - 58	18 - 59
Age groups (years)			
n	63	62	125
18 - 25	16 (25.4%)	23 (37.1%)	39 (31.2%)
> 25 - 45	41 (65.1%)	32 (51.6%)	73 (58.4%)
> 45 - 65	6 (9.5%)	7 (11.3%)	13 (10.4%)
Race			
n	63	62	125
American Indian or Alaska Native	11 (17.5%)	17 (27.4%)	28 (22.4%)
Asian	3 (4.8%)	2 (3.2%)	5 (4.0%)
Black or African American	6 (9.5%)	5 (8.1%)	11 (8.8%)
Multiple	1 (1.6%)	0	1 (0.8%)
Native Hawaiian or other Pacific Islander	1 (1.6%)	0	1 (0.8%)
Unknown	13 (20.6%)	12 (19.4%)	25 (20.0%)
White	28 (44.4%)	26 (41.9%)	54 (43.2%)
Ethnicity			
n	63	62	125
Hispanic or Latino	42 (66.7%)	49 (79.0%)	91 (72.8%)
Not Hispanic or Latino	20 (31.7%)	12 (19.4%)	32 (25.6%)
Not Stated	1 (1.6%)	0	1 (0.8%)
Unknown	0	1 (1.6%)	1 (0.8%)
Height (cm)			
n	63	62	125
Mean (SD)	162.3 (8.21)	160.9 (9.14)	161.6 (8.67)
Median	160.0	160.0	160.0
Q1 - Q3	157.5 - 165.0	154.0 - 167.6	155.0 - 166.0
Min - Max	149 - 189	146 - 184	146 - 189
Weight (kg)			
n	63	62	125
Mean (SD)	69.0 (15.17)	64.2 (14.63)	66.6 (15.04)
Median	66.7	62.7	64.5
Q1 - Q3	58.0 - 80.0	54.5 - 70.6	55.1 - 75.0
Min - Max	44 - 104	41 - 108	41 - 108
BMI (kg/m2)			
n	63	62	125
Mean (SD)	26.21 (5.459)	24.77 (5.091)	25.50 (5.307)
Median	26.04	24.36	24.81
Q1 - Q3	21.88 - 29.41	21.56 - 27.41	21.64 - 28.25
Min - Max	18.1 - 42.2	16.9 - 41.0	16.9 - 42.2
Region			
n	62	61	123
AS*	2 (3.2%)	2 (3.3%)	4 (3.3%)
EU	16 (25.8%)	5 (8.2%)	21 (17.1%)
LAT	37 (59.7%)	46 (75.4%)	83 (67.5%)
US	7 (11.3%)	8 (13.1%)	15 (12.2%)
LN biopsy class			
n	63	62	125
III	14 (22.2%)	17 (27.4%)	31 (24.8%)
IV	49 (77.8%)	45 (72.6%)	94 (75.2%)
Pregnancy			
n	34	33	67
Negative	33 (97.1%)	33 (100.0%)	66 (98.5%)
Positive	1 (2.9%)	0	1 (1.5%)
Duration of SLE (month)			
n	43	40	83
Mean (SD)	84.4 (84.19)	51.2 (50.83)	68.4 (71.68)
Median	57.6	32.3	42.0
Q1 - Q3	16.8 - 131.2	11.5 - 78.0	14.8 - 97.6
Min - Max	1 - 304	3 - 225	1 - 304

	Obi + MMF (N=63)	Placebo + MMF (N=62)	All (N=125)
eGFR(mL/min/1.73m2)			
n	62	62	124
Mean (SD)	102.0 (30.63)	102.1 (32.88)	102.0 (31.65)
Median	106.5	112.0	108.5
Q1 - Q3	85.0 - 126.0	73.0 - 128.0	73.5 - 127.0
Min - Max	39 - 162	26 - 163	26 - 163
Urine RBC(/HPF)			
n	63	62	125
Mean (SD)	10.8 (16.31)	11.5 (26.79)	11.1 (22.05)
Median	4.0	4.0	4.0
Q1 - Q3	1.6 - 13.0	1.0 - 10.0	1.0 - 11.0
Min - Max	0 - 78	0 - 150	0 - 150
Urine WBC(/HPF)			
n	63	62	125
Mean (SD)	11.6 (20.02)	7.1 (9.82)	9.4 (15.90)
Median	4.0	4.0	4.0
Q1 - Q3	2.0 - 10.0	1.0 - 8.0	2.0 - 9.0
Min - Max	0 - 120	0 - 46	0 - 120
Serum creatinine(mg/dL)			
n	63	62	125
Mean (SD)	0.873 (0.3422)	0.799 (0.3259)	0.836 (0.3350)
Median	0.814	0.696	0.769
Q1 - Q3	0.633 - 1.041	0.554 - 0.984	0.588 - 0.984
Min - Max	0.37 - 1.98	0.38 - 2.23	0.37 - 2.23
UPCR(mg/mg)			
n	60	60	120
Mean (SD)	3.318 (2.6628)	2.925 (2.4637)	3.122 (2.5620)
Median	2.726	2.168	2.375
Q1 - Q3	1.591 - 4.178	1.237 - 4.189	1.311 - 4.185
Min - Max	0.25 - 15.76	0.16 - 11.80	0.16 - 15.76
Urine RBC casts			
n	57	58	115
Absent	56 (98.2%)	57 (98.3%)	113 (98.3%)
Present	1 (1.8%)	1 (1.7%)	2 (1.7%)
Smoking			
n	63	62	125
Current	4 (6.3%)	4 (6.5%)	8 (6.4%)
Never	50 (79.4%)	53 (85.5%)	103 (82.4%)
Previous	9 (14.3%)	5 (8.1%)	14 (11.2%)
Prior history of LN	40 (63.5%)	35 (56.5%)	75 (60.0%)
Duration of LN for patients who had prior history of LN (months)			
n	40	35	75
Mean (SD)	61.7 (68.60)	43.0 (50.46)	53.0 (61.15)
Median	36.1	30.0	32.4
Q1 - Q3	14.9 - 85.8	6.6 - 54.5	9.2 - 80.1
Min - Max	1 - 263	1 - 225	1 - 263
Duration of LN calculated from time to biopsy for patients without prior history of LN (months)			
n	23	27	50
Mean (SD)	1.3 (0.82)	1.8 (1.50)	1.6 (1.25)
Median	1.2	1.4	1.3
Q1 - Q3	0.8 - 1.7	0.7 - 2.6	0.8 - 1.9
Min - Max	0 - 3	0 - 6	0 - 6

Obi = Obinutuzumab; MMF = Mycophenolate Mofetil.
SD = Standard Deviation;
n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
US=United States; EU=European Union; LAT=Latin America; AS=Asia;
LN=Lupus Nephritis; SLE = Systemic Lupus Erythematosus; eGFR = Glomerular Filtration Rate; RBC = Red Blood Cells; UPCR = Urine Protein Creatinine Ratio; WBC = White Blood Cells.

Exposure

At study completion, the median duration of obinutuzumab + MMF treatment was 183 days (range: 15–229). The median total dose was 4000.0 mg (range: 2000–4600), with the majority of patients (90.5%) receiving four infusions.

At study completion, the median duration of MMF treatment was 730 days (range: 75–2247) in the obinutuzumab arm and 729 days (range: 4–1247) in the placebo arm. Similarly, the median duration of corticosteroid use was 730.5 days (range: 75–2247) in the obinutuzumab arm and 729 days (range: 114–1247) in the placebo arm.

Results

Table 41 Summary of efficacy results (mITT population)

	Week 52		Week 76		Week 104	
Modified ITT population	**obi + MMF arm n=63**	**placebo + MMF arm n=62**	**obi + MMF arm n=63**	**placebo + MMF arm n=62**	**obi + MMF arm n=63**	**placebo + MMF arm n=62**
CRR						
Responders	22 (34.9%)	14 (22.6%)	24 (38.1%)	11 (17.7%)	27 (42.9%)	14 (22.6%)
non-Responders	41 (65.1%)	48 (77.4%)	39 (61.9%)	51 (82.3%)	36 (57.1%)	48 (77.4%)
Difference	12.3%		20.4%		20.3%	
95% CI	[–3.4%, 28.1%]		[5.0%, 35.7%]		[4.2%, 36.3%]	
80% CI	[2.1%, 22.6%]		[10.3%, 30.4%]		[9.8%, 30.8%]	
p-value [a]	0.1145[b]		0.0109		0.0162	
PRR						
Responders	35 (55.6%)	21 (33.9%)	31 (49.2%)	18 (29.0%)	34 (54.0%)	18 (29.0%)
non-Responders	28 (44.4%)	41 (66.1%)	32 (50.8%)	44 (71.0%)	29 (46.0%)	44 (71.0%)
Difference	21.7%		20.2%		24.9%	
95% CI	[4.7%, 38.7%]		[3.4%, 36.9%]		[8.2%, 41.6%]	
80% CI	[10.6%, 32.8%]		[9.2%, 31.1%]		[14.0%, 35.9%]	
p-value [a]	0.0150 [b]		0.0238		0.0051	
ORR (CRR or PRR)						
Responders	35 (55.6%)	22 (35.5%)	31 (49.2%)	18 (29.0%)	34 (54%)	18 (29%)
non-Responders	28 (44.4%)	40 (64.5%)	32 (50.8%)	44 (71.0%)	29 (46%)	44 (71%)
Difference	20.1%		20.2%		24.9%	
95% CI	[3.0%, 37.2%]		[3.4%, 36.9%]		[8.2%, 41.6%]	
80% CI	[8.9%, 31.3%]		[9.2%, 31.1%]		[14.0%, 35.9%]	
p-value [a]	0.0246[b]		0.0238		0.0051	

	Week 52		Week 76		Week 104	
Modified ITT population	**obi + MMF arm n=63**	**placebo + MMF arm n=62**	**obi + MMF arm n=63**	**placebo + MMF arm n=62**	**obi + MMF arm n=63**	**placebo + MMF arm n=62**
mCRR1						
Responders	25 (39.7%)	16 (25.8%)	29 (46.0%)	14 (22.6%)	32 (50.8%)	14 (22.6%)
non-Responders	38 (60.3%)	46 (74.2%)	34 (54.0%)	48 (77.4%)	31 (49.2%)	48 (77.4%)
Difference	13.9%		23.5%		28.2%	
95% CI	[–2.4%, 30.1%]		[7.3%, 39.6%]		[12.1%, 44.4%]	
80% CI	[3.2%, 24.5%]		[12.9%, 34.0%]		[17.7%, 38.8%]	
p-value [a]	0.0900 [b]		0.0054		0.0012	
mCRR2						
Responders	28 (44.4%)	21 (33.9%)	30 (47.6%)	18 (29.0%)	33 (52.4%)	21 (33.9%)
non-Responders	35 (55.6%)	41 (66.1%)	33 (52.4%)	44 (71.0%)	30 (47.6%)	41 (66.1%)
Difference:	10.6%		18.6%		18.5%	
95% CI:	[–6.4%, 27.6%]		[1.9%, 35.3%]		[1.5%, 35.6%]	
80% CI	[–0.5%, 21.7%]		[7.7%, 29.5%]		[7.4%, 29.7%]	
p-value [a]	0.1838 [b]		0.0271		0.0348	
mCRR3						
Responders	29 (46.0%)	24 (38.7%)	35 (55.6%)	22 (35.5%)	36 (57.1%)	21 (33.9%)
non-Responders	34 (54.0%)	38 (61.3%)	28 (44.4%)	40 (64.5%)	27 (42.9%)	41 (66.1%)
Difference:	7.3%		20.1%		23.3%	
95% CI:	[–10.0%, 24.6%]		[3.0%, 37.2%]		[6.3%, 40.2%]	
80% CI	[–4.0%, 18.6%]		[8.9%, 31.3%]		[12.2%, 34.4%]	
p-value [a]	0.3726		0.0202		0.0089	

Week 52			Week 76		Week 104	
Modified ITT population	**obi + MMF arm n=63**	**placebo + MMF arm n=62**	**obi + MMF arm n=63**	**placebo + MMF arm n=62**	**obi + MMF arm n=63**	**placebo + MMF arm n=62**
Change from baseline in anti-dsDNA (kU/L)						
Mean (SD)	−0.810 (1.054)	−0.076 (1.103)	−0.924 (1.157)	−0.032 (1.157)	−1.034 (1.226)	−0.087 (1.164)
Median	−0.703	−0.047	-0.771	0.000	−1.141	0.000
Q1 - Q3	−1.565–0	−0.691–0.676	−1.723-0	−0.761-0.550	−1.861–0	−0.704–0.496
Min - Max	−4.30–1.45	−2.08–3.09	−4.30-1.21	-2.26-3.32	−4.30–1.95	−2.49–3.58
Adjusted Mean [c] (SE):	−0.848 (0.113)	−0.037 (0.115)	−0.971 (0.117)	0.016 (0.119)	−1.076 (0.128)	−0.043 (0.13)
Difference in Adjusted Mean (95% CI)	−0.81 (−1.13, −0.491)		−0.986 (−1.317, −0.655)		−1.033 (−1.395, −0.672)	
Difference in Adjusted Mean (80% CI)	−0.81 (−1.019, −0.602)		−0.986 (−1.202, −0.771)		−1.033 (−1.269, −0.798)	
p-value [d]:	<.0001 [b]		<.0001		<.0001	

Anti-dsDNA=anti-double-stranded DNA; CI=confidence interval; CRR=complete renal response; ITT=intent to treat; mCRR1=modified complete renal response definition 1; mCRR2=modified complete renal response definition 2; mCRR3=modified complete renal response definition 3; MMF=Mycophenolate Mofetil; Obi=obinutuzumab; ORR=overall renal response; PRR=partial renal response

[a] p value assessed using Cochrane-Mantel-Haenzel (CMH) test

[b] Statistically significant at pre-specified alpha of 20%

[c] A negative change from baseline indicates an improvement

[d] p value assessed using Analysis of Covariance (ANCOVA)

2.4.2. Discussion on clinical efficacy

Gazyvaro (obinutuzumab) was already approved for treatment of Chronic lymphocytic leukaemia (CLL) and Follicular lymphoma (FL). With this procedure, the MAH applied initially to include the following new indication: "*for the treatment of adult patients with active lupus nephritis who are receiving standard therapy*".

The MAH sought scientific advices twice, in 2019 and 2020. In 2019, the MAH sought feedback on filing for extension of indication based on the Phase II NOBILITY study only, which CHMP advised against. Feedback on the study design for the Phase III REGENCY study was provided, and the MAH has complied with elements hereof (endpoint definitions and handling of missing data), but not with proposed stratification factors (Hispanic ethnicity, baseline eGFR and prior response to therapy) or dosing according to baseline values of albumin, IgG or weight. In 2020, follow-up advice on the revised study design for REGENCY study including the split of the obinutuzumab arm in 2-2-2 and 2-2-1 regimen was sought. The CHMP considered that the 2-2-2 and 2-2-1 regimen would add limited value. In both SAs, a clearer definition of how to assess effect of obinutuzumab as induction vs maintenance therapy was recommended.

The application was based on two clinical studies: the pivotal ongoing Phase III REGENCY study and the supportive completed Phase II NOBILITY study.

Concerning dose, no actual dose-response relationships have been investigated, as only one dose (1000 mg i.v.) was provided in both the NOBILITY and REGENCY studies. This dose is similar to the dose of obinutuzumab used in the haemato-oncological setting, where same mechanism of action (B-cell depletion) is sought. However, this dose appeared to be chosen based on a (failed) study assessing rituximab (also anti-CD20 monoclonal antibody) against LN (the LUNAR study) using this dose and dosing schedule (1000 mg x 2 Day 1 and Week 2, 24 and 26). As assessed under PD, a dose of 1000 mg obinutuzumab appeared to provide adequate and sustained B-cell depletion. It remained unexplored whether lower doses of obinutuzumab could have achieved the same responses in LN patients. However, since incomplete B-cell depletion was observed at similar doses of rituximab in LN patients and especially since most adverse effects (except, possibly, neutropenia) are not dose-dependent, the CHMP agreed that no additional dose-finding studies are needed.

Design and conduct of clinical studies

REGENCY study

The pivotal Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter REGENCY study was ongoing at the time of submission and randomized eligible patients 1:1 to receive obinutuzumab (1000 mg IV) or placebo on top of standard of care (mycophenolate mofetil (MMF) 2-2.5 g/day and corticosteroids with a tapering schedule). The obinutuzumab arm was then randomised 1:1 to receive either a "2-2-2-regimen" (obinutuzumab at Week 1+2, 24+26 and 50+52) or a "2-2-1-regimen" (obinutuzumab at Week 1+2, 24+26 and 52, placebo at Week 50). Thus, treatment was double blinded for the period up to Week 76, where the primary outcome was assessed. From Week 76, patients could either 1) continue blinded infusions of obinutuzumab or placebo, if exhibiting an adequate response, 2) in case of inadequate response, transfer to open-label treatment with obinutuzumab (on a 2-2-1-regimen) or 3) enter Study Follow-up (SFU) for at least 12 months from the last dose of obinutuzumab/placebo.

Eligible patients were aged 18-75 years with SLE (based on positive ANA) and biopsy-proven active or active/chronic International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Class III or IV LN with or without concomitant Class V disease. Presence of proteinuria (i.e., UPCR $\geq$1g/g) was required to document clinically active disease in the studies. The eligibility criteria were considered relevant by the CHMP and to reflect LN patients with active Class III or IV LN with or without concomitant Class V disease. Upon the CHMP's request, the MAH agreed to revise the wording of the indication in alignment with the investigated population: *adult patients with active Class III or IV, with or without concomitant Class V, lupus nephritis (LN).*

Standard medications included intravenous methylprednisolone, oral prednisone and MMF. Overall, the posology of methylprednisolone, oral prednisone and MMF were all within the ranges of initial and maintenance doses and tapering regimens suggested in KDIGO 2024 LN guidelines.

MMF is the first-line treatment choice for both induction and maintenance therapy of LN. Upon the CHMP's request, the MAH agreed to revise the wording of the indication to specify the standard therapy received i.e. that Gazyvaro is indicated *in combination with MMF*.

Objectives/Endpoints

The primary objective in the REGENCY study was to evaluate the efficacy of obinutuzumab (both treatment regimens combined) versus placebo. The primary endpoint was a composite endpoint defined as "*Proportion of patients who achieved a complete renal response (CRR) at Week 76, with CRR defined as achievement of all of the following: 24-hour UPCR < 0.5 g/g, 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". This endpoint complied with recommendations in both SAs and focused on control of renal activity as recommended by the Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2013 corr). Rescue therapy was defined as two categories: corticosteroids only, and *other* rescue therapy (including other treatment for LN like cyclophosphamide, anti-CD20 antibodies and calcineurin inhibitors (voclosporin)). The *corticosteroid-only* rescue therapy category included patients who received high dose corticosteroids from Week 64 and onwards defined as methylprednisolone iv >100 mg, or oral prednisolone >20 mg/day for more than 2 weeks, or equivalent doses. The definition of CRR at Week 76 was overall agreed by the CHMP.

Key secondary endpoints included CRR at Week 76 with successful prednisolone taper to max 7.5 mg/day, proteinuric response at Week 76, change in eGFR from baseline to Week 76, death or renal-related events (i.e., treatment failure, worsening proteinuria or eGFR) to Week 76, ORR at Week 50 (defined as either CRR or PRR, the latter being >50% reduction in UPCR from baseline or UPCR<1 g/g, eGFR ≥85% of baseline and no occurrence of the same intercurrent events as in CRR) and, finally, change in FACIT-F scale from baseline to Week 76 (a patient-completed questionnaire with 13 items assessing fatigue, validated in patients with SLE). The relevance of evaluating CRR within patients with successful prednisolone tapering to max 7.5 mg/day was agreed by the CHMP, as the primary endpoint could be achieved with concurrent steroid dosing up to 20 mg/day. Furthermore, assessment of single components of the composite CRR (proteinuric response, eGFR) was also endorsed by the CHMP.

Secondary supportive endpoints included SLE-related laboratory endpoints of change in anti-dsDNA titer from baseline to Week 50 and change in C3 from baseline to Week 50 as well as change in SLEDAI-2K from baseline to Week 76. The SLEDAI-2K measure of global disease activity was considered relevant by the CHMP. This endpoint was also recommended at the first SA, since the inclusion criteria include a diagnosis of SLE and as stated in Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2013 corr): "*If patients with SLE are included, it should be ensured that any benefit in renal functioning is not offset by a deleterious effect on other organs. Therefore, this should be assessed either as a component of a co-primary endpoint or as a key secondary endpoint.* However, the CHMP noted that the use of an organ-specific SLE-score such as BILAG could have elaborated on specific extra-renal effects in addition to a global SLE score such as SLEDAI-2K.

Other exploratory endpoints included descriptive evaluation of the individual components of CRR at Week 76, and change in serology, UPCR, eGFR slope and Global assessment scores at various timepoints up to Week 76. The KDIGO 2024 LN guidelines specify achievement of complete response (by reduction in proteinuria and stabilization/improvement in eGFR) within 6-12 months of starting therapy and these endpoints were thus considered relevant by the CHMP. The other exploratory endpoints of CRR/proteinuric response/ORR at various timepoints beyond Week 76 were considered relevant to support a maintenance claim.

The study originally planned to randomize 252 patients in a 1:1 ratio to receive either obinutuzumab or placebo, with the sample size based on estimates from the Phase II NOBILITY study, where 30% of patients receiving MMF alone and 50% of those receiving obinutuzumab + MMF were expected to achieve CRR at Week 76. This provided 90% power at a two-sided $\alpha = 0.05$ significance level, using a Cochran-Mantel-Haenszel test, stratified by region and race. A protocol amendment later split the obinutuzumab arm into two dosing regimens (2-2-2 and 2-2-1) following FDA recommendations for dose exploration, but the total sample size remained at 252 patients. While the primary and key secondary analyses focused on the pooled obinutuzumab group, a descriptive comparison of the two dosing regimens was also conducted.

Randomization was stratified by region (United States and Canada vs. Latin America and the Caribbean vs. Other) and race (Black vs. Other). Hispanic ethnicity was not included as a stratification factor, despite previous EMA scientific advice, leading to imbalanced Hispanic representation across treatment arms (52.6% in the obinutuzumab 2-2-2 group, 62.5% in the obinutuzumab 2-2-1 group, and 57.6% overall), which may have introduced confounding effects. Additionally, Black patients represented only a ~11-12% of the study population, while the majority (~88%) felt under the broad "Other" category, grouping together diverse racial backgrounds (White, Asian, Indigenous, Mixed), reducing stratification effectiveness and leading to loss of information on potential treatment differences. While a subgroup analysis by race was conducted, the CHMP noted it was limited to Black vs. Other, hence, it would be insufficient to draw conclusions given the small Black patient sample and the known racial differences in LN severity and treatment response.

To assess the robustness of the primary endpoint, multiple sensitivity analyses were conducted, including alternative missing data imputation approaches, different handling of intercurrent events (e.g., excluding early withdrawals, treatment policy strategy), and a tipping point analysis (based on the treatment policy strategy, single imputation instead of multiple imputation, and an unadjusted chi-square test instead of the pre-specified stratified CMH test). However, the CHMP considered that the full analysis population (n=135 in the obinutuzumab arm and 136 patients in the placebo arm) should be retained as the denominators. Instead, only 131 patients in the obinutuzumab arm and 135 patients in the placebo arm were included, suggesting that four patients were excluded from the obinutuzumab arm and 1 in the placebo arm. The MAH clarified that four patients in the obinutuzumab arm and one in the placebo arm who had missing CRR status at Week 76 but did not experience any predefined intercurrent events were handled using a Multiple Imputation by Chained Equations (MICE) with predicted mean matching under a Fully Conditional Specification (FCS) framework, under a Missing At Random (MAR) assumption. The CHMP considered that this hypothetical strategy may have introduced bias, particularly given the imbalance in missingness between arms and the possibility of Missing Not At Random (MNAR). Notably, three of the four missing patients in the obinutuzumab arm were imputed as responders, while the single missing patient in the placebo arm was imputed as a non-responder. This asymmetric handling could theoretically have inflated the estimated treatment effect and influenced statistical significance. However, upon the CHMP's request, the MAH provided detailed clinical data on the five imputed patients, including laboratory data from both before and after week 76, demonstrating that all five patients were imputed correctly, and the imputation strategy did not bias the results in favour of obinutuzumab.

For key secondary endpoints, the analyses followed the SAP, with CMH tests for categorical outcomes (proteinuric response, CRR with prednisone taper, ORR, and death/renal-related events) and appropriate methods for continuous endpoints (eGFR and FACIT-F). A multiplicity strategy was conducted for Type I error control, and sensitivity analyses were performed for missing data.

The first version of the SAP was finalised on August 9, 2021, based on Protocol Version 3 from April 23, 2021, while the first patient was enrolled in August 2020. This means that the study was conducted for a year without a finalised SAP, raising concerns about whether key statistical decisions were fully pre-specified. Upon the CHMP's request, the MAH clarified that the SAP was finalised after patient enrollment but before database lock and unblinding, in accordance with internal procedures. Hence, the issue was not further by the CHMP.

In Protocol Version 3, a multiplicity adjustment strategy was introduced for the first time, along with a new secondary endpoint (proteinuric response at Week 76), which was positioned as the second endpoint in the final multiplicity strategy, tested immediately after CRR with prednisone taper. In Protocol Version 4 (March 2023), CRR with prednisone taper was moved up as the first key secondary endpoint in the testing hierarchy after the primary endpoint. Furthermore, in SAP Version 3 (linked to Protocol Version 5, February 2024), the multiplicity adjustment method was changed from a fixed sequential approach to a fallback method, potentially increasing the chance of demonstrating significance for more endpoints. Upon

the CHMP's request, the MAH clarified that the changes to the endpoint hierarchy and the switch to a fallback multiplicity method were based on input from clinical experts and evolving endpoint relevance, and not influenced by accumulating study data. Hence, the issue was not further pursued by the CHMP.

Design according to indication claim

The design of the study was overall considered adequate. The MAH submitted results of the REGENCY study with a primary endpoint at Week 76, and from the phase of continued blinded obinutuzumab and placebo infusions among adequate responders beyond Week 76 to support a treatment indication implying both induction and maintenance phases.

As laid out in the *EMA Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis* (EMA/CHMP/51230/2013), for the primary outcomes in LN "*Contrary to SLE, a clear distinction between induction and maintenance is generally accepted for lupus nephritis. The minimum optimal duration for assessing outcomes in clinical trials of Class III to V LN should be 3 to 6 months for induction of partial response. A longer period might be needed for induction of complete renal remission, i.e. 1 year. For an agent used for both induction and maintenance an additional 1 year is needed after achieving the response for observing the maintenance of the effect. For a maintenance only claim a 1-year period is reasonable.*"

The design of the REGENCY study consisted of an extended treatment and follow-up of the blinded obinutuzumab arm beyond Week 76. Since the REGENCY study was still ongoing, the data on the patients continuing blinded obinutuzumab treatment beyond Week 76 was limited with small sample sizes (72, 58, 47, 29 and 18 patients in the obinutuzumab arm were included in the Post Week 76 analysis population at Weeks 106, 132, 158, 184 and 210, respectively) and difficulties in comparing continued blinded obinutuzumab with continued blinded placebo treatment due to lack of re-randomisation. The CHMP still acknowledged that sample size of patients within the blinded obinutuzumab arm would not increase with time, as all included patients had reached Week 76, but none had completed the whole study period.

The CHMP concluded that the data available from the randomised phase of the REGENCY study up to Week 76 and the blinded obinutuzumab arm beyond Week 76, were overall considered of a duration sufficient to support the indication of "treatment" i.e. covering both induction and maintenance phases.

NOBILITY study

This completed Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter study was a proof-of-concept study to evaluate safety and efficacy of obinutuzumab versus placebo in patients with LN. After screening, eligible patients were randomized in a 1:1 ratio to receive either obinutuzumab (1000 mg IV) or placebo on top of standard of care (MMF/mycophenolic acid (MPA) and corticosteroids with a tapering schedule) at Week 1+2, 24 and 26. The primary endpoint was assessed at Week 52. Then, patients could continue blinded follow-up until Week 104 (only receiving standard of care treatment, no obinutuzumab/placebo infusions after Week 26). The eligibility criteria for the NOBILITY study were comparable to the REGENCY study and overall considered relevant and to reflect LN patients with active Class III or IV LN with or without concomitant Class V disease.

The primary endpoint was a composite endpoint of CRR at Week 52, not identical to the CRR defined in the REGENCY study, but incorporating the same level of proteinuria (<0.5 g/g) with additional criteria of urinary sediment to assess (lack of) activity and renal function was assessed by serum creatinine rather than eGFR. Secondary endpoints included ORR at Week 52 (CRR or partial renal response (PRR)), modifications of the CRR, time to CRR and proportion of patients achieving CRR/PRR among others. The primary and secondary endpoints were tested at an overall 20% significance level using two-sided hypothesis tests. This was not acceptable to provide statistical significance in a pivotal study, however, this was acceptable for this study designed as a proof-of-concept.

The MAH provided post-hoc analyses of the NOBILITY study to apply the primary and key secondary objectives and endpoints conducted for the REGENCY study. However, the primary assessment was performed on the prespecified analyses within the NOBILITY study.

Efficacy data and additional analyses

REGENCY study

Recruitment and conduct

A total of 271 eligible patients were randomized 1:1 to obinutuzumab or placebo. The obinutuzumab arm was further randomized 1:2 to the 2-2-2 regimen (69 patients) and 2-2-1 regimen (66 patients).

At clinical data cut-off, no patients had completed the study, while discontinuation of the study had occurred for less patients in the obinutuzumab arm compared to the placebo arm (14% vs 25%). Beyond Week 76, the majority of patients continued in the blinded treatment arm (obinutuzumab: 50% vs placebo: 36%), followed by OLT (obinutuzumab: 19% vs placebo: 26%) and SFU (obinutuzumab: 17% vs placebo: 13%).

Up until Week 76, the level of study discontinuations was similar in the two arms (obinutuzumab: 9.6% vs placebo: 11.8%) and primarily related to withdrawals by subject in both arms. Discontinuation of study treatment up to Week 76 was lower in the obinutuzumab arm compared to placebo (obinutuzumab:21% vs placebo: 29%), primarily due to lack of efficacy.

About 40% of all patients experienced major protocol deviations, slightly higher among the patients in the obinutuzumab arm (44%) compared to the placebo arm (37%), with the individual most frequent major protocol deviations reported in comparable frequencies between the arms. The CHMP considered that the major protocol deviations were not expected to have a major impact on study integrity or study results.

Demographics

The randomized population of 271 patients had a median age of 31 years, predominantly female (85%) and enrolled in the region of Latin America/Caribbean (57%). Patients were mostly of white race (48%), followed by American Indian/Alaska Native (19%) or black/African American (15%). These characteristics were evenly distributed in the two treatment arms. Concerning ethnicity, a higher proportion of patients in the placebo group self-reported a Hispanic/Latino ethnicity (63%) compared to the obinutuzumab arm (53%). The patient population was overall considered representative of the target population of patients with LN and is adequately reflected in the SmPC Section 5.1. No relevant differences were noted between the treatment arms except for the lower proportion of Hispanic patients in the obinutuzumab arm.

Baseline disease characteristics and medication history

The included patients were representative of patients with active LN class III-IV and generally the baseline disease characteristics were well balanced between the groups. Most patients had known (prior) LN (obinutuzumab: 60% and placebo: 56%) for a median of 34-36 months in the two arms, while for newly diagnosed LN patients, the median duration of their disease was 0.9 months in both arms. The median 24-hour UPCR was slightly higher in the placebo arm (2.76 g/g) compared to the obinutuzumab arm (2.13 g/g), resulting in more patients of the category of UPCR ≥3 g/g within the placebo group (46%) versus the obinutuzumab group (39%).

Almost all patients had received at least one prior LN treatment (obinutuzumab: 99% vs placebo: 95%), most frequently methylprednisolone (obinutuzumab: 65% vs placebo: 53%), while prednisone had been taken by around 31% in both arms. More patients in the obinutuzumab arm had received prior MMF, cyclophosphamide and azathioprine (46%, 30% and 29%) compared to the placebo arm (34%, 22% and

24%), while receipt of anti-malarial agents was highest in the placebo group (47% vs obinutuzumab: 35%). Only few patients had tried other immune-modulating LN therapy.

Slightly more patients in the obinutuzumab arm (93% and 34%) received concurrent renin-angiotensin-acting agents and lipid-modifying agents versus placebo (83% and 23%). Concerns were raised by the CHMP considering the effects of ACE-inhibitor and lipid-lowering treatment on renal-related outcomes. The MAH clarified that reasonable efforts were made to ensure stable use of these agents throughout the study period and that the magnitude of the effect of RAS-acting and lipid-lowering agents on the primary outcome, if present, would be likely smaller than the observed treatment effect in Regency study. This was agreed by the CHMP.

Furthermore, the CHMP noted that 4 patients in the obinutuzumab arm received azathioprine compared to 1 patient in the placebo arm, of which 2 patients in the obinutuzumab arm started azathioprine treatment after first study treatment (0 in the placebo group). Upon the CHMP's request, the MAH provided additional information about these patients, and, in all cases, it appeared well-justified that azathioprine was used instead of MMF only when the latter was not preferred, and that azathioprine was not used as rescue therapy. The CHMP concluded that the use of azathioprine was unlikely to have influenced the study results.

Exposure

The number of patients receiving the prespecified number of obinutuzumab infusions was equal in the two obinutuzumab regimen arms (2-2-1: 59 patients (43.4%) had received a total of 5 obinutuzumab infusions; 2-2-2: 59 patients (43.4%) a total of 6 infusions).

Primary endpoint

The primary endpoint analysis demonstrated a statistically significant and clinically meaningful improvement in CRR at Week 76 with obinutuzumab versus placebo (adjusted difference in proportions of 13.40% (95% CI 1.95, 24.84)). Sensitivity and supplementary analyses of the primary endpoint supported the findings of the primary analysis, both when using an alternative missing data imputation technique, handling of early study withdrawal as missing data and not as an ICE, and application of treatment policy strategy for all ICEs excluding death. The latter (supplementary analysis based on treatment policy strategy) was, in addition, supported by the results of a pre-specified tipping-point analysis.

There were 15 and 34 patients in the obinutuzumab and placebo arms, respectively, who were considered non-responders based only on experience of an ICE. Most non-responding patients in both arms were assigned to the ICE of treatment failure due to clinical worsening of UPCR/eGFR from Week 24 (obinutuzumab: n=5, placebo: n=21) or receipt of rescue therapy (obinutuzumab: n=3, placebo: n=5). Ten non-responder patients did not have observed data at Week 76. Review of these patients' listings supported the non-responder assumption (2 patients experienced treatment failure due to ESKD; 8 patients experienced treatment failure either due to clinically significant, sustained worsening in UPCR and/or eGFR from Week 24 or receipt of rescue therapy). Timing of ICEs was also assessed and revealed that a substantial subset of the ICEs in both arms occurred at Week 52-76, supporting the notion of sufficient time on treatment before being assigned as non-responder.

Upon the CHMP's request, the MAH provided a post hoc subgroup analysis of CRR of two additional subgroups (Hispanic Y/N and Race) showing a generally consistent treatment benefit in favour of obinutuzumab across the subgroups. However, given the limited sample size and the *post hoc* nature of the analyses, no firm conclusion could be drawn. The CHMP considered that it cannot be fully ruled out that the main positive outcome for obinutuzumab in Regency study is in fact a result of confounding from uneven randomization of Hispanic patients. The CHMP concluded that the risk was sufficiently low and the issue was not further pursued.

Key secondary endpoints

The key secondary endpoints were tested hierarchically to adjust for multiplicity. Both the secondary endpoints of CRR with successful prednisolone taper and proteinuric response at Week 76 were met, i.e., adjusted difference for CRR with successful prednisolone taper of max 7.5 mg/day from Week 64-76: between obinutuzumab and placebo arms of 11.88% (95% CI: 0.57, 23.18), and adjusted difference for proteinuric response (defined as UPCR <0.8 g/g and no ICEs defined as in the primary endpoint) between obinutuzumab and placebo arms of 13.68% (95% CI: 2.01, 25.36). Inclusion of these results in SmPC Section 5.1 was endorsed by the CHMP.

The key secondary endpoint of mean change in eGFR from baseline to Week 76 was not met (adjusted mean of 2.31 vs -1.54 in obinutuzumab vs placebo arm, giving a difference in adjusted means of 3.8, 95% CI: -1.8, 9.5). The statistical significance of subsequent endpoints was automatically rejected, hence, none of the later endpoints were included in the SmPC Section 5.1. Of these, the endpoint of proportion of patients experiencing death or renal-related events (i.e., treatment failure, worsening proteinuria or eGFR) to Week 76 did show a lower proportion of patients in the obinutuzumab arm (19%) vs placebo arm (36%) giving an adjusted difference of −16.83% (95% CI: −27.42, −6.23). The two remaining secondary endpoints of ORR at Week 50 and change in FACIT-F scale from baseline to Week 76 were not met.

Supportive secondary endpoints

Supportive secondary endpoints were not type 1 error-controlled. The included SLE-related laboratory endpoints showed generally greater reduction in anti-dsDNA titers from baseline to Week 50 and greater increase of C3 from baseline to Week 50. Changes in SLEDAI-2K score from baseline to Week 76 were similar between the obinutuzumab and placebo arm. The CHMP concluded that the available data do not indicate that obinutuzumab has deleterious effects on other organs that would offset the benefit on renal function.

Exploratory endpoints

Exploratory endpoints were not type 1 error-controlled. Every individual component of the primary outcome CRR was obtained by most patients in the obinutuzumab arm versus the placebo arm (eGFR>85% of baseline: (84% vs 76%), No occurrence of intercurrent events (89% vs 75%) and UPCR <0.5 g/g (47% vs 36%)). The results on the components of the CRR were considered clinically relevant information on the renal response and, hence, included in the SmPC Section 5.1. eGFR slopes from Week 12 to Week 76 indicated a greater decrease in eGFR over time in the placebo group compared to the obinutuzumab group. Furthermore, the median change in UPCR in the obinutuzumab and placebo arm appeared comparable at both Week 24, Week 50 and Week 76. Finally, the proportion of patients with LN flares between Week 24 and 76 was numerically lower in the obinutuzumab arm compared to placebo.

Obinutuzumab regimens 2-2-1 vs 2-2-2

Descriptive analysis of the obinutuzumab 2-2-2 and 2-2-1 regimens for the primary secondary endpoints showed comparable point estimates of responder rates in the two obinutuzumab arms at Week 76. The sample sizes of the two obinutuzumab arms were not powered to detect statistical difference. However, as the two obinutuzumab regimens were dosed identically up to Week 50, at which point only 2-2-2 received obinutuzumab and 2-2-1 received placebo, followed by an obinutuzumab dose for both regimens at Week 52, evaluation at Week 76 (24 weeks after) was considered to be a short time for proper evaluation of differences in efficacy between the 2 regimens. However, as in discussed in the Clinical pharmacology Section 2.3.5. , the actual difference in CRR occurrence at Week 76 (~4%) was considered minor. The proposed 2-2-1 dosing of obinutuzumab and at every 6 months from Week 52 was accepted by the CHMP.

Blinded obinutuzumab treatment beyond Week 76

Response rates beyond Week 76 both for all included patients and separately for patients deemed adequate responders at Week 76 appeared to support that a substantial proportion of adequate responders at Week 76 maintain CRR on blinded obinutuzumab infusions. SmPC Section 4.2 was updated to indicate that 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.

Subgroup analyses

Subgroup analyses of the primary outcome were limited by small numbers in the individual groups generating very wide confidence intervals. However, comparable effects by point estimates were generally seen regardless of LN disease characteristics and severity (LN class III vs IV, concomitant LN class V, UPCR, ds-DNA, complement C3/C4), region and race. Concerning gender, a tendency towards a negative effect of obinutuzumab was seen for men (adjusted difference of -28.16 (95% CI -53.30, 2.3)). However, the CHMP agreed that the group was small (n=42) and the rate of responders in the placebo group was especially high while the rate of responders within the obinutuzumab group was levelled with the overall point estimate.

Concerning patients with renal impairment, in the very small group of patients with an eGFR of 30-60 mL/min/1.73 m2 (n=31), the efficacy in both the placebo and obinutuzumab group appeared to be low (responders obinutuzumab: 2/12, 16.7%, responders placebo: 5/19, 26.3%, adjusted difference -8.03, 95% CI -34.09, 25.03). Similarly, the 157 patients with a prior history of LN had a markedly lower effect of obinutuzumab (adjusted difference in proportions: 6.03%, 95% CI: -9.19 to 21.25) than the 114 patients with no prior LN (adjusted difference in proportions: 23.75%, 95% CI: 5.73 to 39.81). As discussed by Lichteknert and Anders, 2024[30], LN patients with CKD or prior kidney injury are unlikely to achieve proteinuric response to immunomodulatory drugs due to chronic proteinuria. Hence, the CHMP considered that the selected endpoint of proteinuric response was not well-suited for measuring efficacy in patients with a prior history of LN flares or a reduced GFR. Therefore, the CHMP acknowledged the remaining uncertainty regarding the treatment efficacy in these patients and did not further pursue the issue.

An eGFR<30 mL/min/1.73 m2 was an exclusion criterion and the SmPC sections 4.2 and 4.4 state that the safety and efficacy of Gazyvaro has not been established in patients with severe renal impairment (CrCl < 30 mL/min). This was endorsed by the CHMP.

NOBILITY study

The modified ITT population (mITT) consisted of 125 patients (obinutuzumab: n=63, placebo: n=62).

Baseline demographics were generally well balanced between the arms and representative of the target population.

The primary endpoint (CRR at Week 52) was met by 22 patients (35%) in the obitutuzumab arm compared to 14 patients (23%) in the placebo group, resulting in an adjusted difference in proportions of 12.3% (80% CI: [2.1%, 22.6%], p=0.1145). The secondary endpoints of ORR (CRR or PRR) at Week 52, and CRR in various modifications at Week 52 all showed numerically higher proportions of responders in the obinutuzumab arm compared to the placebo arm.

The results of the NOBILITY study were overall considered supportive of the findings in the REGENCY study.

[30] Lichtnekert, Julia, and Hans-Joachim Anders. "Lupus nephritis-related chronic kidney disease." *Nature Reviews Rheumatology* 20.11 (2024): 699-711.

No dose adjustment is required in elderly patients. SmPC Sections 4.2 and 4.4 were updated to indicate that the safety and efficacy of obinuzumab in patients with LN above 65 years of age have not been established.

2.4.3. Conclusions on the clinical efficacy

The pivotal REGENCY study, ongoing at the time of submission, is a Phase III randomized, double-blind, placebo-controlled, parallel-group, multicentre study of obinutuzumab versus placebo on top of standard of care (MMF and corticosteroids with a tapering schedule) in patients with Class III or IV LN with or without concomitant Class V disease. Patients in the obinutuzumab arm were further randomized to receive obinutuzumab (1000 mg iv) in two different dosing regimens, however, all efficacy analyses were conducted on the combined group. The study met its primary endpoint of complete renal response at Week 76. Key secondary endpoints were tested hierarchically and the endpoints of CRR with successful steroid taper, and proteinuric response were also met. The differences between obinutuzumab and placebo arms were considered clinically relevant. The CHMP agreed to recommend Gazyvaro in combination with MMF for the treatment of adult patients with active Class III or IV, with or without concomitant Class V, LN under the following regimen: 1000 mg iv at Week 1, 2, 24, 26, 52 and every 6 months hereafter.

2.5. Clinical safety

Introduction

Three pooled safety analyses were reported:

- Week 76 safety analysis: this pools safety data from the 76-week double blind, placebo-controlled treatment period in REGENCY and the 52-week double blind, placebo-controlled treatment period plus an additional 24 weeks of investigator blinded study follow-up in NOBILITY.
- Primary Data Cut safety analysis: this pools safety data from 76-week double blind, placebo-controlled treatment period in REGENCY and the 52-week double-blind, placebo-controlled treatment period in NOBILITY.
- All Exposure safety analysis: this pools safety data from REGENCY and NOBILITY up until patients' last dose of obinutuzumab or placebo +6 months, the CCOD, or study withdrawal (whichever occurred first).

All three pooled safety analyses were performed using the pooled safety-evaluable population, defined as patients who received any part of blinded infusion of obinutuzumab or placebo in REGENCY or NOBILITY. Patients who were randomized in either study but who did not receive any part of blinded infusion of obinutuzumab or placebo were not included in the pooled safety-evaluable population. Patients were grouped according to the treatment that they actually received rather than the treatment assigned.

Table 42 Study contribution to the pooled Week 76 safety analysis

Study	Placebo-Controlled Treatment Period	Obinutuzumab Contribution	Placebo Contribution
REGENCY	76 weeks	76-week double-blind, placebo-controlled treatment period	76-week double-blind, placebo-controlled treatment period
NOBILITY	52 weeks	52-week double-blind, placebo-controlled treatment period + 24-week investigator-blinded SFU	52-week double-blind, placebo-controlled treatment period + 24-week investigator-blinded SFU

SFU = study follow-up.

Table 43 Study contribution to the pooled primary data cut safety analysis

Study	Placebo-Controlled Treatment Period	Obinutuzumab Contribution	Placebo Contribution
REGENCY	76 weeks	76-week double-blind, placebo-controlled treatment period	76-week double-blind, placebo-controlled treatment period
NOBILITY	52 weeks	52-week double-blind, placebo-controlled treatment period	52-week double-blind, placebo-controlled treatment period

Table 44 Study contribution to the pooled all exposure safety analysis

Study	Length of Primary Treatment Period	Obinutuzumab Contribution		Placebo Contribution	
		Primary Treatment Period	After Week 76	Primary Treatment Period	After Week 76
REGENCY	76 weeks	76-week double-blind, placebo-controlled treatment period: last obinutuzumab dose + 6 months	Patients randomized to obinutuzumab who achieved adequate response at Week 76 [a] and continued blinded infusions: last obinutuzumab dose +6 months Patients randomized to obinutuzumab or placebo who achieved inadequate response at Week 76 [b] and entered OLT: last obinutuzumab dose +6 months	76-week double-blind, placebo-controlled treatment period: last placebo dose + 6 months	Patients randomized to placebo who achieved adequate response at Week 76 [a] and continued blinded infusions: last placebo dose +6 months
NOBILITY	52 weeks	Last obinutuzumab dose +6 months	N/A	Last placebo dose + 6 months	N/A

OLT = open-label treatment.

[a] See Table 2 for details on study treatment in REGENCY after Week 76.

[b] In REGENCY, patients randomized to placebo at Day 1 who achieved an inadequate treatment response at the Week 76 primary analysis switched to open-label obinutuzumab. These patients therefore contribute safety data to the pooled obinutuzumab All Exposure arm following their first dose after switching to obinutuzumab treatment in the OLT period. Patients who switched from placebo to obinutuzumab were re-baselined as of their first dose of obinutuzumab during the OLT period.

Standard therapies in Regency and Nobility studies are provided in Table 11.

Patient exposure

Table 45 Exposure to Obinutuzumab in the pooled Week 76 and all exposure populations

	Week 76 (N=200)	All Exposure [a] (N=239)
Treatment duration (days)		
N	200	239
Mean (SD)	281.5 (112.7)	496.8 (371.4)
Median	364.0	368.0
Min – Max	1–415	1–1352
Number of infusions		
N	200	239
Mean (SD)	4.7 (1.2)	6.1 (2.9)
Median	5.0	6.0
Min – Max	1–6	1–13
Number of infusions category, n (%)		
N	200	239
1	4 (2.0)	6 (2.5)
2	9 (4.5)	16 (6.7)
3	3 (1.5)	5 (2.1)
4	66 (33.0)	71 (29.7)
5	59 (29.5)	19 (7.9)
6	59 (29.5)	24 (10.0)
7	0	21 (8.8)
8	0	22 (9.2)
9	0	16 (6.7)
10	0	22 (9.2)
11	0	7 (2.9)
12	0	5 (2.1)
13	0	5 (2.1)

OLT=open-label treatment.

Note: Treatment duration is the difference between the date of the last dose and the date of the first dose plus one day.

[a] REGENCY study patients who received placebo on Day 1 and switched to obinutuzumab treatment during the OLT period are counted in both arms for exposure in the All Exposure safety analysis. The treatment duration and number of infusions for such patients is calculated according to the corresponding first dose of placebo at randomization and the first dose of obinutuzumab at the beginning of OLT period. See Section 1.2.6.1. As of the CCOD, 39 patients in REGENCY had switched from blinded placebo to open-label obinutuzumab treatment.

Blinded Obinutuzumab exposure (safety-evaluable patients) in REGENCY study is provided in Table 21.

Table 46 Exposure for the first 52 weeks in Nobility study (safety population)

	Obi + MMF (N=64)
Treatment duration (days)	
n	63
Mean (SD)	173.7 (42.51)
Median	183.0
Q1 - Q3	181.0 - 184.0
Min - Max	15 - 229
Total dose (mg)	
n	63
Mean (SD)	3849.9 (522.83)
Median	4000.0
Q1 - Q3	4000.0 - 4000.0
Min - Max	2000 - 4600
Number of Infusions	
n	63
2	4 (6.3%)
3	2 (3.2%)
4	57 (90.5%)

Obi = Obinutuzumab; MMF = Mycophenolate Mofetil.
SD = Standard Deviation;
n represents number of patients with non-missing result.
Treatment duration is calculated as difference between date of last dose and date of first dose plus one day.
Analysis data-cut have been applied.

Table 47 Patient disposition in the pooled Week 76 population (safety analysis set)

Status	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Randomized patients	200 (100%)	193 (100%)	393 (100%)
Treated patients	200 (100%)	193 (100%)	393 (100%)
Completed treatment	138 (69.0%)	120 (62.2%)	258 (65.6%)
Discontinued from treatment	35 (17.5%)	46 (23.8%)	81 (20.6%)
Adverse event	8 (4.0%)	5 (2.6%)	13 (3.3%)
Death	3 (1.5%)	2 (1.0%)	5 (1.3%)
Lack of efficacy	7 (3.5%)	24 (12.4%)	31 (7.9%)
Physician decision	5 (2.5%)	6 (3.1%)	11 (2.8%)
Pregnancy	3 (1.5%)	0	3 (0.8%)
Withdrawal by subject	7 (3.5%)	6 (3.1%)	13 (3.3%)
Other	2 (1.0%)	3 (1.6%)	5 (1.3%)
Completed week 76	182 (91.0%)	161 (83.4%)	343 (87.3%)
Discontinued from study on or prior to week 76	18 (9.0%)	32 (16.6%)	50 (12.7%)
Adverse event	0	2 (1.0%)	2 (0.5%)
Death	4 (2.0%)	5 (2.6%)	9 (2.3%)
Lack of efficacy	1 (0.5%)	1 (0.5%)	2 (0.5%)
Lost to follow-up	1 (0.5%)	4 (2.1%)	5 (1.3%)
Non-compliance with study drug	1 (0.5%)	0	1 (0.3%)
Physician decision	0	5 (2.6%)	5 (1.3%)
Post trial access	1 (0.5%)	0	1 (0.3%)
Receipt of additional therapies that reduce peripheral B-Cell counts	0	2 (1.0%)	2 (0.5%)
Withdrawal by subject	10 (5.0%)	12 (6.2%)	22 (5.6%)
Other	0	1 (0.5%)	1 (0.3%)

Only discontinuations on or before Week 76 are captured.
Completed treatment represent the subjects who completed all the intended treatment doses.
Completed week 76 represent the subjects who completed the week 76 period.

Table 48 Patient demographics in the pooled Week 76 population

	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Sex			
n	200	193	393
Male	29 (14.5%)	32 (16.6%)	61 (15.5%)
Female	171 (85.5%)	161 (83.4%)	332 (84.5%)
Age (yr)			
n	200	193	393
Mean (SD)	33.00 (10.24)	32.51 (10.08)	32.76 (10.15)
Median	31.00	31.00	31.00
Min - Max	18.0 - 64.0	18.0 - 72.0	18.0 - 72.0
Age group (yr)			
n	200	193	393
<65	200 (100%)	192 (99.5%)	392 (99.7%)
>=65	0	1 (0.5%)	1 (0.3%)
Race			
n	200	193	393
American Indian or Alaska Native	36 (18.0%)	43 (22.3%)	79 (20.1%)
Asian	12 (6.0%)	9 (4.7%)	21 (5.3%)
Black or African American	26 (13.0%)	25 (13.0%)	51 (13.0%)
Native Hawaiian or other Pacific Islander	1 (0.5%)	0	1 (0.3%)
White	95 (47.5%)	87 (45.1%)	182 (46.3%)
Multiple	12 (6.0%)	9 (4.7%)	21 (5.3%)
Not Reported	1 (0.5%)	3 (1.6%)	4 (1.0%)
Unknown	17 (8.5%)	17 (8.8%)	34 (8.7%)
Geographic Region			
n	200	193	393
United States and Canada	27 (13.5%)	27 (14.0%)	54 (13.7%)
Latin America and the Caribbean	116 (58.0%)	123 (63.7%)	239 (60.8%)
Other	57 (28.5%)	43 (22.3%)	100 (25.4%)
Ethnicity			
n	200	193	393
Hispanic or Latino	114 (57.0%)	131 (67.9%)	245 (62.3%)
Not Hispanic or Latino	75 (37.5%)	58 (30.1%)	133 (33.8%)
Not Reported	10 (5.0%)	1 (0.5%)	11 (2.8%)
Unknown	1 (0.5%)	3 (1.6%)	4 (1.0%)
Height (cm)			
n	200	193	393
Mean (SD)	162.16 (9.03)	161.67 (9.13)	161.92 (9.07)
Median	161.00	160.00	161.00
Min - Max	123.0 - 189.0	140.0 - 188.0	123.0 - 189.0
Weight (kg)			
n	200	193	393
Mean (SD)	67.03 (14.40)	67.14 (15.42)	67.08 (14.89)
Median	65.75	65.00	65.00
Min - Max	36.7 - 106.3	41.0 - 133.6	36.7 - 133.6

Table 49 Baseline disease characteristics in the pooled Week 76 population

	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Serum Creatinine (umol/L)			
n	200	193	393
Mean (SD)	74.8 (32.78)	75.2 (38.85)	75.0 (35.84)
Median	71.0	65.0	68.0
Min - Max	30 - 332	24 - 388	24 - 388
eGFR (mL/min/1.73m2)			
n	199	193	392
Mean (SD)	102.5 (29.53)	102.4 (32.48)	102.4 (30.98)
Median	107.0	111.0	108.0
Min - Max	15 - 164	13 - 166	13 - 166
24-hour Urine Protein/Creatinine Ratio (mg/mg)			
n	196	191	387
Mean (SD)	3.2 (2.93)	3.3 (2.61)	3.2 (2.77)
Median	2.3	2.6	2.4
Min - Max	0 - 22	0 - 13	0 - 22
24-hour Urine Protein/Creatinine Ratio (mg/mg) category			
n	196	191	387
<3	117 (59.7%)	112 (58.6%)	229 (59.2%)
>=3	79 (40.3%)	79 (41.4%)	158 (40.8%)
anti-dsDNA (kU/L) category			
n	200	193	393
<=120	114 (57.0%)	107 (55.4%)	221 (56.2%)
>120	86 (43.0%)	86 (44.6%)	172 (43.8%)
C3 Complement (g/L) category			
n	200	193	393
<0.9	122 (61.0%)	110 (57.0%)	232 (59.0%)
>=0.9	78 (39.0%)	83 (43.0%)	161 (41.0%)
C4 Complement (g/L) category			
n	200	192	392
<0.1	52 (26.0%)	57 (29.7%)	109 (27.8%)
>=0.1	148 (74.0%)	135 (70.3%)	283 (72.2%)
Serum Albumin (g/L)			
n	200	193	393
Mean (SD)	33.7 (6.22)	33.5 (6.30)	33.6 (6.25)
Median	35.0	34.0	34.0
Min - Max	16 - 46	15 - 46	15 - 46
Baseline Lupus Nephritis (LN) class			
n	200	193	393
Class III	70 (35.0%)	67 (34.7%)	137 (34.9%)
Class IV	130 (65.0%)	126 (65.3%)	256 (65.1%)
Prior history of LN			
n	200	193	393
Yes	121 (60.5%)	110 (57.0%)	231 (58.8%)
No	79 (39.5%)	83 (43.0%)	162 (41.2%)
Duration of LN for patients who had prior history of LN (months)			
n	121	110	231
Mean (SD)	64.3 (75.20)	53.7 (60.85)	59.3 (68.81)
Median	36.6	30.5	34.9
Min - Max	0 - 330	1 - 225	0 - 330
Duration of LN calculated from time to biopsy for patients who did not have prior history of LN (months)			
n	79	83	162
Mean (SD)	1.5 (1.44)	1.5 (1.30)	1.5 (1.37)
Median	1.0	1.1	1.1
Min - Max	0 - 7	0 - 6	0 - 7
SLEDAI - 2K			
n	200	193	393
Mean (SD)	12.1 (7.28)	12.3 (6.18)	12.2 (6.75)
Median	10.5	12.0	12.0
Min - Max	4 - 83	0 - 35	0 - 83

Adverse events

In both REGENCY and NOBILITY, verbatim AE terms were mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and AE severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Table 50 Overview of deaths and adverse events in the pooled Week 76 population

	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of patients with at least one AE	183 (91.5%)	171 (88.6%)	354 (90.1%)
Total number of AEs	1096	936	2032
Total number of deaths	4 (2.0%)	1 (0.5%)	5 (1.3%)
Total number of patients discontinued from study due to an AE	1 (0.5%)	3 (1.6%)	4 (1.0%)
Total number of patients with at least one			
AE with fatal outcome	4 (2.0%)	3 (1.6%)	7 (1.8%)
Grade 3-5 AE	62 (31.0%)	38 (19.7%)	100 (25.4%)
AE leading to discontinuation from blinded Obi or MMF	13 (6.5%)	11 (5.7%)	24 (6.1%)
AE leading to discontinuation from blinded Obi	11 (5.5%)	8 (4.1%)	19 (4.8%)
AE leading to discontinuation from MMF	3 (1.5%)	5 (2.6%)	8 (2.0%)
AE leading to blinded Obi or MMF infusion modification/interruption	101 (50.5%)	69 (35.8%)	170 (43.3%)
AE leading to blinded Obi infusion modification/interruption	29 (14.5%)	19 (9.8%)	48 (12.2%)
AE leading to MMF infusion modification/interruption	91 (45.5%)	62 (32.1%)	153 (38.9%)
AE related to blinded Obi or MMF	121 (60.5%)	87 (45.1%)	208 (52.9%)
AE related to blinded Obi	100 (50.0%)	62 (32.1%)	162 (41.2%)
AE related to MMF	93 (46.5%)	68 (35.2%)	161 (41.0%)
Serious AE	57 (28.5%)	39 (20.2%)	96 (24.4%)
Serious AE leading to discontinuation from blinded Obi or MMF	10 (5.0%)	8 (4.1%)	18 (4.6%)
Serious AE leading to discontinuation from blinded Obi	9 (4.5%)	7 (3.6%)	16 (4.1%)
Serious AE leading to discontinuation from MMF	2 (1.0%)	2 (1.0%)	4 (1.0%)
Serious AE leading to blinded Obi or MMF infusion modification/interruption	41 (20.5%)	17 (8.8%)	58 (14.8%)
Serious AE leading to blinded Obi infusion modification/interruption	4 (2.0%)	3 (1.6%)	7 (1.8%)
Serious AE leading to MMF infusion modification/interruption	41 (20.5%)	17 (8.8%)	58 (14.8%)
Serious AE related to blinded Obi or MMF	24 (12.0%)	16 (8.3%)	40 (10.2%)
Serious AE related to blinded Obi	22 (11.0%)	12 (6.2%)	34 (8.7%)
Serious AE related to MMF	20 (10.0%)	15 (7.8%)	35 (8.9%)
AEs of special interest			
Hy s Law	0	0	0
Suspected transmission of an infectious agent by the study drug	0	0	0
Infusion related reactions	30 (15.0%)	21 (10.9%)	51 (13.0%)
Grade 3 or higher infections	23 (11.5%)	19 (9.8%)	42 (10.7%)
Any Hepatitis B reactivation and PML	0	0	0
Drug related Neutropenia	20 (10.0%)	7 (3.6%)	27 (6.9%)
Drug related Thrombocytopenia	1 (0.5%)	0	1 (0.3%)
Gastrointestinal perforations	1 (0.5%)	1 (0.5%)	2 (0.5%)
Worsening of pre-existing cardiac conditions (*)	0	2 (1.0%)	2 (0.5%)

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, end of study or receipt of rescue therapy (whichever occurs first).
(*) 'Worsening of pre-existing cardiac conditions' AESI includes REGENCY (CA41705) study data only.

Common AEs

Table 51 Adverse events with ≥5% incidence in either treatment arm by preferred term in the pooled Week 76 population

MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of patients with at least one adverse event	161 (80.5%)	134 (69.4%)	295 (75.1%)
Total number of events	433	399	832
COVID-19	38 (19.0%)	31 (16.1%)	69 (17.6%)
URINARY TRACT INFECTION	34 (17.0%)	26 (13.5%)	60 (15.3%)
DIARRHOEA	30 (15.0%)	26 (13.5%)	56 (14.2%)
INFUSION RELATED REACTION	27 (13.5%)	20 (10.4%)	47 (12.0%)
BRONCHITIS	25 (12.5%)	14 (7.3%)	39 (9.9%)
UPPER RESPIRATORY TRACT INFECTION	21 (10.5%)	18 (9.3%)	39 (9.9%)
HERPES ZOSTER	14 (7.0%)	17 (8.8%)	31 (7.9%)
HEADACHE	18 (9.0%)	12 (6.2%)	30 (7.6%)
GASTROENTERITIS	11 (5.5%)	18 (9.3%)	29 (7.4%)
NASOPHARYNGITIS	14 (7.0%)	14 (7.3%)	28 (7.1%)
NAUSEA	14 (7.0%)	14 (7.3%)	28 (7.1%)
ARTHRALGIA	13 (6.5%)	14 (7.3%)	27 (6.9%)
HYPERTENSION	14 (7.0%)	12 (6.2%)	26 (6.6%)
VOMITING	10 (5.0%)	14 (7.3%)	24 (6.1%)
ABDOMINAL PAIN	9 (4.5%)	14 (7.3%)	23 (5.9%)
ANAEMIA	12 (6.0%)	11 (5.7%)	23 (5.9%)
NEUTROPENIA	17 (8.5%)	6 (3.1%)	23 (5.9%)
INFLUENZA	11 (5.5%)	10 (5.2%)	21 (5.3%)
INSOMNIA	8 (4.0%)	10 (5.2%)	18 (4.6%)
PNEUMONIA	10 (5.0%)	6 (3.1%)	16 (4.1%)
PYREXIA	6 (3.0%)	10 (5.2%)	16 (4.1%)
COUGH	10 (5.0%)	3 (1.6%)	13 (3.3%)

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which
multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, end of study or receipt of rescue therapy (whichever occurs
first).

Table 52 Adverse events by SOC, pooled Week 76 population

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of patients with at least one adverse event	183 (91.5%)	171 (88.6%)	354 (90.1%)
Overall total number of events	1096	936	2032
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	144 (72.0%)	119 (61.7%)	263 (66.9%)
Total number of events	368	306	674
GASTROINTESTINAL DISORDERS			
Total number of patients with at least one adverse event	69 (34.5%)	67 (34.7%)	136 (34.6%)
Total number of events	135	136	271
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total number of patients with at least one adverse event	36 (18.0%)	44 (22.8%)	80 (20.4%)
Total number of events	54	72	126
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Total number of patients with at least one adverse event	45 (22.5%)	33 (17.1%)	78 (19.8%)
Total number of events	59	42	101
NERVOUS SYSTEM DISORDERS			
Total number of patients with at least one adverse event	38 (19.0%)	34 (17.6%)	72 (18.3%)
Total number of events	49	47	96
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Total number of patients with at least one adverse event	34 (17.0%)	32 (16.6%)	66 (16.8%)
Total number of events	46	40	86
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total number of patients with at least one adverse event	30 (15.0%)	32 (16.6%)	62 (15.8%)
Total number of events	37	44	81
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one adverse event	33 (16.5%)	26 (13.5%)	59 (15.0%)
Total number of events	55	41	96
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total number of patients with at least one adverse event	35 (17.5%)	21 (10.9%)	56 (14.2%)
Total number of events	46	26	72
METABOLISM AND NUTRITION DISORDERS			
Total number of patients with at least one adverse event	23 (11.5%)	27 (14.0%)	50 (12.7%)
Total number of events	38	33	71
INVESTIGATIONS			
Total number of patients with at least one adverse event	28 (14.0%)	18 (9.3%)	46 (11.7%)
Total number of events	49	27	76
VASCULAR DISORDERS			
Total number of patients with at least one adverse event	25 (12.5%)	19 (9.8%)	44 (11.2%)
Total number of events	27	22	49

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
PSYCHIATRIC DISORDERS			
Total number of patients with at least one adverse event	17 (8.5%)	21 (10.9%)	38 (9.7%)
Total number of events	26	27	53
RENAL AND URINARY DISORDERS			
Total number of patients with at least one adverse event	21 (10.5%)	14 (7.3%)	35 (8.9%)
Total number of events	28	14	42
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Total number of patients with at least one adverse event	17 (8.5%)	9 (4.7%)	26 (6.6%)
Total number of events	23	9	32
EYE DISORDERS			
Total number of patients with at least one adverse event	13 (6.5%)	10 (5.2%)	23 (5.9%)
Total number of events	18	13	31
CARDIAC DISORDERS			
Total number of patients with at least one adverse event	10 (5.0%)	8 (4.1%)	18 (4.6%)
Total number of events	11	8	19
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
Total number of patients with at least one adverse event	8 (4.0%)	7 (3.6%)	15 (3.8%)
Total number of events	9	9	18
ENDOCRINE DISORDERS			
Total number of patients with at least one adverse event	6 (3.0%)	4 (2.1%)	10 (2.5%)
Total number of events	6	4	10
HEPATOBILIARY DISORDERS			
Total number of patients with at least one adverse event	5 (2.5%)	5 (2.6%)	10 (2.5%)
Total number of events	6	7	13
IMMUNE SYSTEM DISORDERS			
Total number of patients with at least one adverse event	3 (1.5%)	3 (1.6%)	6 (1.5%)
Total number of events	4	3	7
EAR AND LABYRINTH DISORDERS			
Total number of patients with at least one adverse event	0	4 (2.1%)	4 (1.0%)
Total number of events	0	5	5
CONGENITAL, FAMILIAL AND GENETIC DISORDERS			
Total number of patients with at least one adverse event	0	1 (0.5%)	1 (0.3%)
Total number of events	0	1	1
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	2	0	2

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, study withdrawal or receipt of rescue therapy (whichever occurs first).

Treatment-related adverse events

Table 53 Adverse events related to blinded Obinutuzumab with ≥5% incidence in either treatment arm in the pooled Week 76 population

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of patients with at least one adverse event	100 (50.0%)	62 (32.1%)	162 (41.2%)
Overall Total number of events	248	168	416
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	61 (30.5%)	40 (20.7%)	101 (25.7%)
Total number of events	128	88	216
URINARY TRACT INFECTION	16 (8.0%)	10 (5.2%)	26 (6.6%)
HERPES ZOSTER	10 (5.0%)	10 (5.2%)	20 (5.1%)
BRONCHITIS	12 (6.0%)	7 (3.6%)	19 (4.8%)
UPPER RESPIRATORY TRACT INFECTION	10 (5.0%)	6 (3.1%)	16 (4.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Total number of patients with at least one adverse event	28 (14.0%)	20 (10.4%)	48 (12.2%)
Total number of events	31	25	56
INFUSION RELATED REACTION	27 (13.5%)	20 (10.4%)	47 (12.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one adverse event	16 (8.0%)	8 (4.1%)	24 (6.1%)
Total number of events	30	12	42
NEUTROPENIA	12 (6.0%)	4 (2.1%)	16 (4.1%)

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, end of study or receipt of rescue therapy (whichever occurs first).

Grade 3-4 AEs

Grade 3-4 adverse events were reported by 58 patients (29.0%) in the obinutuzumab arm and 35 patients (18.1%) in the placebo arm.

Table 54 NCI CTCAE Grade 3-4 adverse events by SOC and PTs (≥ 2% of patients in either arm), pooled Week 76 population

MedDRA System Organ Class **MedDRA Preferred Term**	**Obinutuzumab** **(N=200)**	**Placebo** **(N=193)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Neutropenia	8 (4.0%)	0
INFECTIONS AND INFESTATIONS		
COVID-19	4 (2.0%)	0
COVID-19 Pneumonia	4 (2.0%)	0
Pneumonia	2 (1.0%)	4 (2.1%)
Gastroenteritis	4 (2.0%)	4 (2.1%)
Urinary Tract Infection	6 (3.0%)	3 (1.6%)
Herpes Zoster	0	4 (2.1%)

Investigator text for AEs encoded using MedDRA version 27.0.

All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.

To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.

Percentages are based on N in the column headings.

Includes AEs with onset from first dose of study drug until week 76, end of study or receipt of rescue therapy (whichever occurs first).

Serious adverse event/deaths/other significant events

Deaths

As of the CCOD in REGENCY and the final analysis in NOBILITY, there were 7 deaths in the obinutuzumab arm and 8 deaths in the placebo arm in the pooled safety evaluable population, as per patients' original randomization assignment and with no truncation rules applied.

Following application of data cuts and truncation rules in the three pooled safety analyses, there are some differences between the number of deaths and the number of fatal AEs within each pooled population. In addition, in the pooled All Exposure population, deaths of 2 patients in REGENCY who were originally randomized to the placebo arm are presented in the obinutuzumab arm, as these patients switched to open-label obinutuzumab after Week 76 and prior to their deaths.

The deaths reported in Table 47 corresponded to the following fatal events (by PT, Table 48):

- COVID-19 pneumonia (2 patients), death (1 patient), nephrotic syndrome (1 patient) in the obinutuzumab arm. The patient with the PT "death" (reported term "died due to an unknown cause") died during the 24 week follow-up period in NOBILITY.
- COVID-19 (1 patient) in the placebo arm.

In addition, in the placebo arm, there was 1 patient in REGENCY with fatal AE onset (PT: B-cell lymphoma) during the 76 week treatment period but who died after the Week 76 data cut, and 1 patient in NOBILITY with fatal AE onset (PT: systemic lupus erythematosus) prior to receipt of rescue medication but who died after receipt of rescue medication.

The fatal AEs for COVID-19 and B-cell lymphoma were assessed by the investigator as being related to study treatment, whereas the fatal AEs of nephrotic syndrome, death, and systemic lupus erythematosus were assessed as unrelated to study treatment

Table 55 Overview of Deaths in the Pooled Week 76 Population

Summary of Deaths, Week 76 Safety Analysis Set
Protocol: CA41705, WA29748

	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of deaths	4 (2.0%)	1 (0.5%)	5 (1.3%)
Primary cause of death			
n	4	1	5
Adverse event	4 (100%)	1 (100%)	5 (100%)
Progressive disease	0	0	0
Other	0	0	0

Percentages for Total Number of Deaths are relative to total N.
All other percentages are relative to n within each module.
Includes deaths from first dose of study drug until week 76, end of study or receipt of rescue therapy (whichever occurs first).

Table 56 Fatal Adverse Events in the Pooled Week 76 Population

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of Deaths	4 (2.0%)	3 (1.6%)	7 (1.8%)
Overall Total number of events	4	3	7
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	2 (1.0%)	1 (0.5%)	3 (0.8%)
Total number of events	2	1	3
COVID-19 PNEUMONIA	2 (1.0%)	0	2 (0.5%)

COVID-19	0	1 (0.5%)	1 (0.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
DEATH	1 (0.5%)	0	1 (0.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total number of patients with at least one adverse event	0	1 (0.5%)	1 (0.3%)
Total number of events	0	1	1
SYSTEMIC LUPUS ERYTHEMATOSUS	0	1 (0.5%)	1 (0.3%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
Total number of patients with at least one adverse event	0	1 (0.5%)	1 (0.3%)
Total number of events	0	1	1
B-CELL LYMPHOMA	0	1 (0.5%)	1 (0.3%)
RENAL AND URINARY DISORDERS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
NEPHROTIC SYNDROME	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, end of study or receipt of rescue therapy (whichever occurs first).

Serious adverse events (SAEs)

Table 57 SAEs with ≥2% incidence in either treatment arm in the pooled Week 76 population

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of patients with at least one adverse event	57 (28.5%)	39 (20.2%)	96 (24.4%)
Overall Total number of events	89	67	156
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	25 (12.5%)	19 (9.8%)	44 (11.2%)
Total number of events	38	28	66
PNEUMONIA	5 (2.5%)	4 (2.1%)	9 (2.3%)
COVID-19 PNEUMONIA	7 (3.5%)	0	7 (1.8%)
URINARY TRACT INFECTION	5 (2.5%)	2 (1.0%)	7 (1.8%)
COVID-19	4 (2.0%)	1 (0.5%)	5 (1.3%)
HERPES ZOSTER	0	4 (2.1%)	4 (1.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one adverse event	6 (3.0%)	1 (0.5%)	7 (1.8%)
Total number of events	10	1	11
NEUTROPENIA	5 (2.5%)	0	5 (1.3%)

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, end of study or receipt of rescue therapy (whichever occurs first).

Adverse events of Special interest (AESI)

Hy's law

There were no cases of Hy's Law in either treatment arm (Week 76 safety analysis).

Suspected Transmission of an Infectious Agent by the Study Drug

There were no cases of suspected transmission of an infectious agent by the study drug in either treatment arm.

Infusion-related reactions (IRRs):

Due to the broad definition of the AESI of IRR (includes the PT of infusion related reaction, events that occurred within 24 hours of an infusion, and AEs that had the IRR AESI flag ticked on the CRF), not all PTs reported in the IRR summary tables are necessarily 'true' IRRs. However, to avoid excluding any potential IRRs and for completeness of data presentation, all PTs were retained.

Table 58 AESI of infusion-related reactions in the pooled Week 76 population

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of patients with at least one adverse event	30 (15.0%)	21 (10.9%)	51 (13.0%)
Overall Total number of events	35	26	61
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Total number of patients with at least one adverse event	28 (14.0%)	20 (10.4%)	48 (12.2%)
Total number of events	31	25	56
INFUSION RELATED REACTION	27 (13.5%)	20 (10.4%)	47 (12.0%)
INCORRECT DRUG ADMINISTRATION RATE	1 (0.5%)	0	1 (0.3%)
GASTROINTESTINAL DISORDERS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
NAUSEA	1 (0.5%)	0	1 (0.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total number of patients with at least one adverse event	0	1 (0.5%)	1 (0.3%)
Total number of events	0	1	1
FATIGUE	0	1 (0.5%)	1 (0.3%)
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
BRONCHITIS	1 (0.5%)	0	1 (0.3%)
NERVOUS SYSTEM DISORDERS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
HEADACHE	1 (0.5%)	0	1 (0.3%)
VASCULAR DISORDERS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
HYPERTENSION	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, study withdrawal or receipt of rescue therapy (whichever occurs first).
Includes the IRR preferred terms, events that occurred within 24 hours of infusion, and AEs that had the IRR AESI flag ticked on eCRF.

Table 59 Infusion-related adverse events by Grade, Week 76 safety analysis set

- Infusion: 1

MedDRA System Organ Class MedDRA Preferred Term	Grade	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
- Any adverse events -	- Any Grade -	21 (10.5%)	12 (6.2%)	33 (8.4%)
	Grade 1-2	19 (9.5%)	11 (5.7%)	30 (7.6%)
	1	12 (6.0%)	6 (3.1%)	18 (4.6%)
	2	7 (3.5%)	5 (2.6%)	12 (3.1%)
	Grade 3-4	2 (1.0%)	1 (0.5%)	3 (0.8%)
	3	1 (0.5%)	1 (0.5%)	2 (0.5%)
	4	1 (0.5%)	0	1 (0.3%)

- Infusion: 2

MedDRA System Organ Class MedDRA Preferred Term	Grade	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
- Any adverse events -	- Any Grade -	6 (3.0%)	6 (3.1%)	12 (3.1%)
	Grade 1-2	5 (2.5%)	6 (3.1%)	11 (2.8%)
	1	4 (2.0%)	5 (2.6%)	9 (2.3%)
	2	1 (0.5%)	1 (0.5%)	2 (0.5%)
	Grade 3-4	1 (0.5%)	0	1 (0.3%)
	3	1 (0.5%)	0	1 (0.3%)

Applying the methodology for determination of adverse drug reactions (ADRs) in the SmPC (methodology described at the end of this Section), it was found that IRRs were reported in 13.5% of patients in the obinutuzumab arm vs 10.4% of patients in the placebo arm. Grade 3-4 IRRs were reported in 1.5% of patients in the obinutuzumab arm vs 0.5% of patients in the placebo arm.

IRRs in both arms were predominantly Grade 1-2 and occurred during/after the first infusion. All Grade 3-4 events occurred during/after either the first or second infusion. The incidence and severity of IRRs decreased with subsequent infusions. In the Regency study, the most common IRR signs/symptoms included headache, nausea and vomiting. In the Nobility study, the most common IRR symptoms were pyrexia and tachycardia.

Infections:

Infections were reported in 72.0% of patients in the Gazyvaro arm vs. 61.7% of patients in the placebo arm. The most frequently reported infections were upper and lower respiratory tract infections.

Table 60 AESI of Grade 3-5 infections in the pooled Week 76 population

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of patients with at least one adverse event	23 (11.5%)	19 (9.8%)	42 (10.7%)
Overall Total number of events	37	30	67
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	22 (11.0%)	19 (9.8%)	41 (10.4%)
Total number of events	34	29	63
URINARY TRACT INFECTION	6 (3.0%)	3 (1.6%)	9 (2.3%)
GASTROENTERITIS	4 (2.0%)	4 (2.1%)	8 (2.0%)
COVID-19 PNEUMONIA	6 (3.0%)	0	6 (1.5%)
PNEUMONIA	2 (1.0%)	4 (2.1%)	6 (1.5%)
COVID-19	4 (2.0%)	1 (0.5%)	5 (1.3%)
HERPES ZOSTER	0	4 (2.1%)	4 (1.0%)
PYELONEPHRITIS	0	2 (1.0%)	2 (0.5%)
UROSEPSIS	1 (0.5%)	1 (0.5%)	2 (0.5%)
BACTERIAL DIARRHOEA	0	1 (0.5%)	1 (0.3%)
BACTERIAL INFECTION	1 (0.5%)	0	1 (0.3%)
BRONCHITIS	0	1 (0.5%)	1 (0.3%)
CYTOMEGALOVIRUS CHORIORETINITIS	0	1 (0.5%)	1 (0.3%)
CYTOMEGALOVIRUS MYOCARDITIS	0	1 (0.5%)	1 (0.3%)
DEVICE RELATED BACTERAEMIA	0	1 (0.5%)	1 (0.3%)
DISSEMINATED CYTOMEGALOVIRAL INFECTION	0	1 (0.5%)	1 (0.3%)
GASTROENTERITIS VIRAL	1 (0.5%)	0	1 (0.3%)
INFLUENZA	1 (0.5%)	0	1 (0.3%)
KLEBSIELLA BACTERAEMIA	0	1 (0.5%)	1 (0.3%)
MENINGITIS CRYPTOCOCCAL	0	1 (0.5%)	1 (0.3%)
ORAL CANDIDIASIS	1 (0.5%)	0	1 (0.3%)
PERITONSILLAR ABSCESS	1 (0.5%)	0	1 (0.3%)
POST-ACUTE COVID-19 SYNDROME	1 (0.5%)	0	1 (0.3%)
PYELONEPHRITIS ACUTE	0	1 (0.5%)	1 (0.3%)
RESPIRATORY TRACT INFECTION	1 (0.5%)	0	1 (0.3%)
SARS-COV-2 SEPSIS	1 (0.5%)	0	1 (0.3%)
TUBERCULOSIS	1 (0.5%)	0	1 (0.3%)
URETHRITIS	1 (0.5%)	0	1 (0.3%)
VARICELLA	0	1 (0.5%)	1 (0.3%)
GASTROINTESTINAL DISORDERS			
Total number of patients with at least one adverse event	0	1 (0.5%)	1 (0.3%)
Total number of events	0	1	1
INTESTINAL PERFORATION	0	1 (0.5%)	1 (0.3%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
VULVOVAGINAL WARTS	1 (0.5%)	0	1 (0.3%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
CERVICAL DYSPLASIA	1 (0.5%)	0	1 (0.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
ORGANISING PNEUMONIA	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, end of study or receipt of rescue therapy (whichever occurs first).

Hepatitis B or progressive multifocal leukoencephalopathy

There were no cases of hepatitis B reactivation or PML in either treatment arm (Week 76 safety analysis).

Neutropenia:

Neutropenia was represented by grouping together 3 specific PTs (neutropenia, febrile neutropenia and neutrophil count decreased) in the pooled week 76 population, irrespective of seriousness or reporter causality:

- PT Neutropenia: 17 patients in obinutuzumab arm vs 6 patients in placebo arm
- PT Febrile neutropenia: 1 patient in obinutuzumab arm vs 0 patients in placebo arm
- PT Neutrophil count decreased: 4 patients in obinutuzumab arm vs 1 patient in placebo arm.

Thus, the total number of patients reporting these PTs was 22 patients in obinutuzumab arm vs 7 patients in placebo arm.

For the determination of adverse drug reaction in the SmPC, the MAH conservatively grouped the PTs of Neutropenia, Leukopenia, Lymphopenia, Lymphocyte count decreased, Febrile neutropenia and Neutrophil Count decreased. Therefore, the number of patients experiencing 'Neutropenia' as a broad medical concept using these PTs in the pooled Week 76 Safety-Evaluable population, irrespective of reporter causality, was 28 patients (14.0%) in obinutuzumab arm vs 12 patients (6.2%) in placebo arm. Grade 3-4 neutropenia was reported in 7% of patients treated with obinutuzumab vs 0.5% of patients in the placebo arm.

The number of patients with drug-related neutropenia AESI events in the pooled week 76 population is presented in Table 61.

Table 61 AESI of drug-related neutropenia in the pooled Week 76 population

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of patients with at least one adverse event	20 (10.0%)	7 (3.6%)	27 (6.9%)
Overall Total number of events	28	9	37
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one adverse event	18 (9.0%)	6 (3.1%)	24 (6.1%)
Total number of events	26	7	33
NEUTROPENIA	17 (8.5%)	6 (3.1%)	23 (5.9%)
LEUKOPENIA	2 (1.0%)	0	2 (0.5%)
FEBRILE NEUTROPENIA	1 (0.5%)	0	1 (0.3%)
INVESTIGATIONS			
Total number of patients with at least one adverse event	2 (1.0%)	1 (0.5%)	3 (0.8%)
Total number of events	2	2	4
NEUTROPHIL COUNT DECREASED	2 (1.0%)	1 (0.5%)	3 (0.8%)

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, study withdrawal or receipt of rescue therapy (whichever occurs first).

The number of patients with serious drug-related neutropenia events was higher in the obinutuzumab arm (6 of 20 patients) than the placebo arm (0 of 7 patients). As of the data cut, all events of serious drug-related neutropenia, including the single event of Grade 4 febrile neutropenia, had resolved. A total of 11 patients in the obinutuzumab arm and 3 patients in placebo arm in the pooled Week 76 population received G-CSF.

Thrombocytopenia

The AESI of drug-related thrombocytopenia was reported in 1 patient (0.5%) in the obinutuzumab arm (Week 76 safety analysis). The event was serious, Grade 4, and assessed by the investigator as related to study treatment. As of the data cut, the event had resolved.

Worsening of pre-existing cardiac conditions (AESI for REGENCY only)

In REGENCY, no patients in the obinutuzumab arm experienced worsening of pre existing cardiac conditions. In the placebo arm, 2 patients (1.5%) experienced worsening of pre-existing cardiac conditions, reported as pericardial effusion (1 patient [0.8%]) and sinus tachycardia (1 patient [0.8%]). Both events were Grade 2, non serious, and resolved without any reported intervention.

Laboratory findings

Table 62 Laboratory abnormalities, Week 76 safety analysis set

Laboratory Test	Direction of Abnormality	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Hematology				
Basophils, Abs	High	8/193 (4.1%)	4/191 (2.1%)	12/384 (3.1%)
Eosinophils, Abs	High	1/198 (0.5%)	1/191 (0.5%)	2/389 (0.5%)
Hematocrit	Low	42/134 (31.3%)	43/131 (32.8%)	85/265 (32.1%)
	High	7/197 (3.6%)	6/190 (3.2%)	13/387 (3.4%)
Hemoglobin	Low	37/ 91 (40.7%)	33/ 89 (37.1%)	70/180 (38.9%)
	High	2/198 (1.0%)	1/193 (0.5%)	3/391 (0.8%)
Lymphocytes, Atypical, Abs	High	17/ 17 (100%)	11/ 11 (100%)	28/ 28 (100%)
Lymphocytes Abs	Low	87/147 (59.2%)	67/142 (47.2%)	154/289 (53.3%)
	High	3/195 (1.5%)	7/189 (3.7%)	10/384 (2.6%)
Ery. Mean Corpuscular Hemoglobin	Low	23/183 (12.6%)	17/180 (9.4%)	40/363 (11.0%)
	High	1/198 (0.5%)	0/192	1/390 (0.3%)
Ery. Mean Corpuscular Volume	Low	22/190 (11.6%)	15/186 (8.1%)	37/376 (9.8%)
	High	22/170 (12.9%)	25/168 (14.9%)	47/338 (13.9%)
Monocytes, Abs	Low	13/195 (6.7%)	17/186 (9.1%)	30/381 (7.9%)
	High	19/194 (9.8%)	12/193 (6.2%)	31/387 (8.0%)
Neutrophils, Total, Abs	Low	51/191 (26.7%)	43/187 (23.0%)	94/378 (24.9%)
	High	68/154 (44.2%)	57/150 (38.0%)	125/304 (41.1%)
Platelet	Low	11/191 (5.8%)	6/186 (3.2%)	17/377 (4.5%)
	High	47/180 (26.1%)	33/172 (19.2%)	80/352 (22.7%)
Erythrocytes	Low	26/ 80 (32.5%)	42/ 82 (51.2%)	68/162 (42.0%)
	High	6/198 (3.0%)	4/193 (2.1%)	10/391 (2.6%)
Total Leukocyte Count	Low	63/183 (34.4%)	57/177 (32.2%)	120/360 (33.3%)
	High	50/162 (30.9%)	43/159 (27.0%)	93/321 (29.0%)
Immunology				
Immunoglobulin A	Low	9/194 (4.6%)	2/184 (1.1%)	11/378 (2.9%)
	High	6/175 (3.4%)	11/175 (6.3%)	17/350 (4.9%)
Immunoglobulin G	Low	28/137 (20.4%)	21/143 (14.7%)	49/280 (17.5%)
	High	2/182 (1.1%)	16/176 (9.1%)	18/358 (5.0%)
Immunoglobulin M	Low	66/160 (41.3%)	22/161 (13.7%)	88/321 (27.4%)
	High	2/188 (1.1%)	1/184 (0.5%)	3/372 (0.8%)

Laboratory Test	Direction of Abnormality	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Chemistry				
Albumin	Low	16/130 (12.3%)	26/114 (22.8%)	42/244 (17.2%)
	High	7/198 (3.5%)	7/193 (3.6%)	14/391 (3.6%)
Alkaline Phosphatase	Low	10/183 (5.5%)	17/181 (9.4%)	27/364 (7.4%)
	High	37/188 (19.7%)	19/179 (10.6%)	56/367 (15.3%)
SGPT/ALT	Low	2/198 (1.0%)	5/193 (2.6%)	7/391 (1.8%)
	High	31/192 (16.1%)	25/180 (13.9%)	56/372 (15.1%)
Amylase	Low	0/ 24	0/ 20	0/ 44
	High	1/ 13 (7.7%)	2/ 14 (14.3%)	3/ 27 (11.1%)
SGOT/AST	Low	4/196 (2.0%)	2/192 (1.0%)	6/388 (1.5%)
	High	27/195 (13.8%)	21/183 (11.5%)	48/378 (12.7%)
Blood Urea Nitrogen	Low	0/198	0/193	0/391
	High	22/151 (14.6%)	31/152 (20.4%)	53/303 (17.5%)
Calcium	Low	24/163 (14.7%)	42/161 (26.1%)	66/324 (20.4%)
	High	0/198	3/192 (1.6%)	3/390 (0.8%)
Chloride	Low	2/197 (1.0%)	3/191 (1.6%)	5/388 (1.3%)
	High	7/196 (3.6%)	13/190 (6.8%)	20/386 (5.2%)
Cholesterol	Low	44/188 (23.4%)	39/185 (21.1%)	83/373 (22.3%)
	High	50/115 (43.5%)	30/105 (28.6%)	80/220 (36.4%)
Creatine Kinase	Low	33/146 (22.6%)	36/142 (25.4%)	69/288 (24.0%)
	High	29/197 (14.7%)	30/190 (15.8%)	59/387 (15.2%)
Creatinine	Low	4/197 (2.0%)	2/192 (1.0%)	6/389 (1.5%)
	High	18/173 (10.4%)	26/167 (15.6%)	44/340 (12.9%)
Glucose	Low	36/191 (18.8%)	38/176 (21.6%)	74/367 (20.2%)
	High	73/176 (41.5%)	42/163 (25.8%)	115/339 (33.9%)
Lactate Dehydrogenase	Low	0/198	0/192	0/390
	High	53/140 (37.9%)	43/138 (31.2%)	96/278 (34.5%)
Triacylglycerol Lipase	High	0/ 20	0/ 17	0/ 37
Phosphorus	Low	10/197 (5.1%)	7/190 (3.7%)	17/387 (4.4%)
	High	33/184 (17.9%)	39/183 (21.3%)	72/367 (19.6%)
Potassium	Low	32/172 (18.6%)	40/183 (21.9%)	72/355 (20.3%)
	High	5/196 (2.6%)	3/191 (1.6%)	8/387 (2.1%)
Sodium	Low	5/196 (2.6%)	5/190 (2.6%)	10/386 (2.6%)
	High	5/196 (2.6%)	7/192 (3.6%)	12/388 (3.1%)
Bilirubin	Low	65/138 (47.1%)	57/127 (44.9%)	122/265 (46.0%)
	High	4/194 (2.1%)	1/186 (0.5%)	5/380 (1.3%)
Protein, Total	Low	36/ 76 (47.4%)	36/ 72 (50.0%)	72/148 (48.6%)
	High	0/197	3/193 (1.6%)	3/390 (0.8%)
Triglycerides	Low	1/198 (0.5%)	5/192 (2.6%)	6/390 (1.5%)
	High	40/105 (38.1%)	39/104 (37.5%)	79/209 (37.8%)
Uric Acid	Low	3/198 (1.5%)	2/193 (1.0%)	5/391 (1.3%)
	High	25/165 (15.2%)	32/160 (20.0%)	57/325 (17.5%)

Table entries provide the number of patients with a during treatment laboratory value abnormality in the direction specified among patients without this abnormality at baseline.
Abnormalities reported in patients with missing baseline values are included.
Baseline is the patient's last observation prior to initiation of study drug.
Includes laboratory data from first dose of study drug until week 76, study withdrawal or receipt of rescue therapy (whichever occurs first).

Safety in special populations

Race (Black vs. Other)

Of the 393 safety-evaluable patients in the pooled Week 76 population, 43 patients (21 in the obinutuzumab arm; 22 in the placebo arm) were Black and 350 patients (179 in the obinutuzumab arm; 171 in the placebo arm) were of Other race.

Region (United States and Canada vs. Latin America and the Caribbean vs. Other)

Subgroup analyses were performed in the pooled Week 76 and Primary Data Cut populations to evaluate the consistency of the safety profile of obinutuzumab between regions in the categories of United States and Canada, Latin America and the Caribbean, and Other. Of the 393 safety-evaluable patients in the pooled Week 76 population, 54 patients (27 in each of the obinutuzumab and placebo arms) were from the United States and Canada, 239 patients (116 in the obinutuzumab arm; 123 in the placebo arm) were from Latin America and the Caribbean, and 100 patients (57 in the obinutuzumab arm; 43 in the placebo arm) were from Other regions.

The proportion of patients with at least one AE in the obinutuzumab arm was slightly higher in Other regions (56 patients [98.2%]) as compared with the United States and Canada (25 patients [92.6%]) and Latin American and the Caribbean (102 patients [87.9%]).

The most frequently reported AEs by SOC were Infections and Infestations in all regions. These AEs were balanced between the United States and Canada (20 patients [74.1%]) and Other regions (44 patients [77.2%]) in the obinutuzumab arm, but were slightly lower in Latin America and the Caribbean (80 patients [69.0%]).

Safety related to drug-drug interactions and other interactions

No formal drug-drug or drug-food interaction studies have been performed for obinutuzumab in the LN or haemato-oncology indications. However, limited haemato-oncology drug-drug interaction substudies have been undertaken for obinutuzumab with bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), and FC (fludarabine, cyclophosphamide) and chlorambucil. Co-administration with obinutuzumab had no effect on the pharmacokinetics of bendamustine, FC, chlorambucil or the individual components of CHOP; in addition, there were no apparent effects of bendamustine, FC, chlorambucil, or CHOP on the pharmacokinetics of obinutuzumab. As already stated in the SmPC Section 4.5, a risk for interactions with concomitantly used medicinal products cannot be excluded.

Discontinuation due to adverse events

Table 63 Adverse events leading to blinded obinutuzumab discontinuation by SOC and PT in the pooled Week 76 population

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of patients with at least one adverse event	11 (5.5%)	8 (4.1%)	19 (4.8%)
Overall Total number of events	15	11	26
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	4 (2.0%)	4 (2.1%)	8 (2.0%)
Total number of events	4	7	11
URINARY TRACT INFECTION	0	2 (1.0%)	2 (0.5%)
COVID-19	0	1 (0.5%)	1 (0.3%)
CYTOMEGALOVIRUS CHORIORETINITIS	0	1 (0.5%)	1 (0.3%)
CYTOMEGALOVIRUS MYOCARDITIS	0	1 (0.5%)	1 (0.3%)
DISSEMINATED CYTOMEGALOVIRAL INFECTION	0	1 (0.5%)	1 (0.3%)
MENINGITIS CRYPTOCOCCAL	0	1 (0.5%)	1 (0.3%)
POST-ACUTE COVID-19 SYNDROME	1 (0.5%)	0	1 (0.3%)
SKIN INFECTION	1 (0.5%)	0	1 (0.3%)
TOOTH INFECTION	1 (0.5%)	0	1 (0.3%)
URETHRITIS	1 (0.5%)	0	1 (0.3%)
RENAL AND URINARY DISORDERS			
Total number of patients with at least one adverse event	2 (1.0%)	3 (1.6%)	5 (1.3%)
Total number of events	3	3	6
ACUTE KIDNEY INJURY	0	1 (0.5%)	1 (0.3%)
GLOMERULONEPHRITIS	1 (0.5%)	0	1 (0.3%)
LUPUS NEPHRITIS	0	1 (0.5%)	1 (0.3%)
NEPHROTIC SYNDROME	1 (0.5%)	0	1 (0.3%)
PROTEINURIA	0	1 (0.5%)	1 (0.3%)
TUBULOINTERSTITIAL NEPHRITIS	1 (0.5%)	0	1 (0.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one adverse event	3 (1.5%)	0	3 (0.8%)
Total number of events	3	0	3
NEUTROPENIA	2 (1.0%)	0	2 (0.5%)
FEBRILE NEUTROPENIA	1 (0.5%)	0	1 (0.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
INFUSION RELATED REACTION	1 (0.5%)	0	1 (0.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
SYSTEMIC LUPUS ERYTHEMATOSUS	1 (0.5%)	0	1 (0.3%)

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
Total number of patients with at least one adverse event	0	1 (0.5%)	1 (0.3%)
Total number of events	0	1	1
B-CELL LYMPHOMA	0	1 (0.5%)	1 (0.3%)
NERVOUS SYSTEM DISORDERS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
AUTOIMMUNE ENCEPHALOPATHY	1 (0.5%)	0	1 (0.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
ORGANISING PNEUMONIA	1 (0.5%)	0	1 (0.3%)
VASCULAR DISORDERS			
Total number of patients with at least one adverse event	1 (0.5%)	0	1 (0.3%)
Total number of events	1	0	1
HYPERTENSION	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, end of study or receipt of rescue therapy (whichever occurs first).

Dose modification of blinded obinutuzumab was not permitted in REGENCY or NOBILITY; however, the rate of infusion could be adjusted in the event of an IRR. Blinded obinutuzumab infusions could also be slowed or withheld for patients who experienced toxicity considered to be related to study drug in both REGENCY and NOBILITY.

Table 64 Adverse events leading to blinded Obinutuzumab dose interruption, Week 76 safety analysis set

MedDRA System Organ Class MedDRA Preferred Term	Obinutuzumab (N=200)	Placebo (N=193)	All Patients (N=393)
Total number of patients with at least one adverse event	29 (14.5%)	19 (9.8%)	48 (12.2%)
Overall Total number of events	34	30	64
INFECTIONS AND INFESTATIONS			
Total number of patients with at least one adverse event	11 (5.5%)	14 (7.3%)	25 (6.4%)
Total number of events	12	17	29
COVID-19	1 (0.5%)	5 (2.6%)	6 (1.5%)
URINARY TRACT INFECTION	3 (1.5%)	2 (1.0%)	5 (1.3%)
HERPES ZOSTER	1 (0.5%)	1 (0.5%)	2 (0.5%)
PNEUMONIA	1 (0.5%)	1 (0.5%)	2 (0.5%)
CELLULITIS	1 (0.5%)	0	1 (0.3%)
COVID-19 PNEUMONIA	1 (0.5%)	0	1 (0.3%)
DEVICE RELATED BACTERAEMIA	0	1 (0.5%)	1 (0.3%)
EPSTEIN-BARR VIRUS INFECTION	0	1 (0.5%)	1 (0.3%)
INFECTIOUS MONONUCLEOSIS	0	1 (0.5%)	1 (0.3%)
INFLUENZA	0	1 (0.5%)	1 (0.3%)
LOWER RESPIRATORY TRACT INFECTION	1 (0.5%)	0	1 (0.3%)
ORAL HERPES	1 (0.5%)	0	1 (0.3%)
PHARYNGITIS	0	1 (0.5%)	1 (0.3%)
PYELONEPHRITIS	0	1 (0.5%)	1 (0.3%)
RASH PUSTULAR	1 (0.5%)	0	1 (0.3%)
SKIN INFECTION	1 (0.5%)	0	1 (0.3%)
TONSILLITIS	0	1 (0.5%)	1 (0.3%)
UPPER RESPIRATORY TRACT INFECTION	0	1 (0.5%)	1 (0.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Total number of patients with at least one adverse event	14 (7.0%)	2 (1.0%)	16 (4.1%)
Total number of events	14	2	16
INFUSION RELATED REACTION	13 (6.5%)	2 (1.0%)	15 (3.8%)
INCORRECT DRUG ADMINISTRATION RATE	1 (0.5%)	0	1 (0.3%)
NERVOUS SYSTEM DISORDERS			
Total number of patients with at least one adverse event	0	3 (1.6%)	3 (0.8%)
Total number of events	0	3	3
HEADACHE	0	2 (1.0%)	2 (0.5%)
IDIOPATHIC INTRACRANIAL HYPERTENSION	0	1 (0.5%)	1 (0.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total number of patients with at least one adverse event	2 (1.0%)	0	2 (0.5%)
Total number of events	2	0	2
NEUTROPENIA	1 (0.5%)	0	1 (0.3%)
THROMBOCYTOPENIA	1 (0.5%)	0	1 (0.3%)

Investigator text for AEs encoded using MedDRA version 27.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug until week 76, end of study or receipt of rescue therapy (whichever occurs first).

Program: root/clinical_studies/RO5072759/CDPT3787/share/pool_safety/prod/program/t_ae.sas
Output: root/clinical_studies/RO5072759/CDPT3787/share/pool_safety/prod/output/t_ae_DINBOBI_WK76SE.out
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Adverse Drug Reactions (ADR)

For labelling purposes, ADRs were identified based on the AEs observed in all obinutuzumab-treated patients from REGENCY and NOBILITY in the pooled Week 76 safety analysis.

Firstly, all AEs in obinutuzumab-treated patients, irrespective of severity (i.e., all Grades 1-5), were reviewed, and an appropriate threshold of ≥ 2% difference in incidence between the obinutuzumab and placebo arms was determined. Those AEs with a ≥ 2% difference in incidence were then selected for further systematic review. In addition, relevant AEs were grouped together by medical concept where appropriate (e.g., different reported PTs for infections of the upper respiratory tract were grouped together under a single medical concept of "upper respiratory tract infections"). The incidence of grouped AEs representing the medical concept is expressed as the percentage of patients who experienced at least one of these grouped AEs.

Following identification of individual and grouped AEs for further review, medical and scientific judgement was used to assess whether each individual AE/grouped AEs qualified as an ADR. Individual patient-level review of all selected AEs and grouped AEs was performed to establish causality with obinutuzumab (e.g., identifying risk factors, alternative explanations for the AEs, latency, and assessing treatment details etc.). All available evidence, including understanding whether the underlying disease or the mode of action of obinutuzumab could have contributed to the AEs, comparison with same in class molecules, and

application of Bradford-Hill Criteria, was taken into account to establish the ADRs associated with obinutuzumab in patients with lupus nephritis.

Table 65 Summary of initially proposed adverse drug reactions in the pooled Week 76 population

MedDRA SOC/ADR	Grades 3–5 (%)	All Grades (%)	Frequency Category (All Grades)
Infections and Infestations			
Upper respiratory tract infection	0	29.0	Very common
COVID-19	5.0	22.5	Very common
Urinary tract infection	3.0	21.0	Very common
Bronchitis	0	14.0	Very common
Pneumonia	2.0	9.5	Common
Herpes simplex	0	2.5	Common
Injury, Poisoning and Procedural Complications			
Infusion related reaction	1.5	13.5	Very common
Blood and Lymphatic System Disorders			
Neutropenia	7.0	14.0	Very common

ADR = adverse drug reaction; CIOMS = Council for International Organizations of Medical Sciences; SOC = System Organ Class.

Note: CIOMS III ADR frequency categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to 1/1000); very rare (< 1/10,000).

In addition, during the procedure, blood immunoglobulin M decreased (all grades) was identified as adverse reaction at the frequency very common (Frequency category derived from laboratory values collected as part of routine laboratory monitoring in clinical trials).

Post marketing experience

No new safety concerns were identified for any of the approved obinutuzumab indications based on post-marketing data from the reporting interval of the most recent Periodic Benefit-Risk Evaluation Report (PBRER; 1 November 2020 to 31 October 2023

2.5.1. Discussion on clinical safety

The safety evaluation of obinutuzumab in LN was based on the pooled safety data from a total of 393 safety-evaluable patients enrolled in the pivotal Phase III Regency study and supportive Phase II Nobility study.

The Week 76 safety pool (results from both Regency and Nobility) was considered the main safety pool. The 2+2+1 pool (Arm 2) of the Regency study consisted in 67 patients who received five 1000 mg IV doses on day 1, weeks 2, 24, 26, and 52, this corresponds to the proposed dosing regimen. The 2+2+2 pool (Arm 1) of the Regency study consisted of 69 patients, who received six 1000 mg IV doses (one additional dose on week 50 compared to the 2+2+1 pool). In the Nobility study, four 1000 mg IV doses were given (last dose given on week 26). For the latter pool, safety was followed by investigator up to week 76, corresponding to the so-called primary treatment period in the Regency study. The placebo pool consisted of 132 patients from the Regency study and 61 patients from the Nobility study corresponding to 193 placebo treated patients.

The all-exposure population included patients who crossed over to the obinutuzumab arms in the Regency study (n=39), and cutoff was last dose of obinutuzumab or placebo +6 months, the clinical cut-off date, or study withdrawal (whichever occurred first).

All patients received standard backbone treatment.

The median duration of treatment with obinutuzumab was 364.0 days (range: 1-415 days) in the pooled Week 76 population. The median number of obinutuzumab infusions was 5.0 (range: 1-6 infusions). In the Regency study, 43% of participants received 5 doses (Arm 2) and 43% received 6 doses (Arm 1). In the Nobility study, 91% of participants received the maximum of 4 doses. Overall, the exposure was considered sufficient.

With regards to disposition, the main difference was a higher rate of discontinuation in the placebo arm due to lack of efficacy. Demographic characteristics and baseline disease characteristics were generally well balanced between treatment arms in the pooled Week 76 population.

Most patients in both arms experienced at least one AE.

The most frequently reported AEs by SOC were Infections and Infestations (72.0% in obinutuzumab pool and 61.7% in the placebo pool). The second most frequently reported AEs by SOC were Gastrointestinal Disorders, which were similar between the two groups (34.5% in obinutuzumab pool versus 34.7% in placebo pool) and were mostly driven by diarrhoea. In the SOC Respiratory disorders, the frequency was higher in the obinutuzumab pool compared to the placebo pool (17.5% and 10.9%, respectively).

Grade 3-4 AEs were more frequent in the obinutuzumab pool compared to the placebo pool (29.0% and 18.1%, respectively).

At week 76, there were four deaths (fatal events) in the obinutuzumab arm (2 due to COVID-19, one to nephrotic syndrome and one to an unknown cause) and 3 deaths (fatal events) in the placebo arm at week 76 (one due to COVID-19, one to B-cell lymphoma and one due to SLE).

The frequency of SAEs was higher in the obinutuzumab pool compared to the placebo pool (28.5% vs. 20.2%, respectively). The majority of SAEs in the obinutuzumab pool were under the SOC infectionsE. and infestations, the higher frequency (12.5% and 9.8%, respectively) was due to COVID-19 (including pneumonia) with a 5.5% frequency in the obinutuzumab pool compared to 0.5% in the placebo pool. All COVID-19 infections occurred in the Regency study. Infections are further discussed hereafter under *AESI*.

Adverse events of special interest (AESI):

IRRs:

IRRs were reported in 13.5% of patients in the obinutuzumab arm vs 10.4% of patients in the placebo arm. Grade 3-4 IRRs were reported in 1.5% of patients in the Gazyvaro arm vs 0.5% of patients in the placebo arm. Most were Grade 1-2 events, and all Grade 3-4 IRRs occurred in conjunction with either the first or second infusion. A warning was included in the SmPC Section 4.4 to inform on the risk of IRR. SmPC Section 4.2 includes information on the management of IRR. Further, IRR were included as adverse reactions Section 4.8 of the SmPC (frequency very common for all grades, frequency common for grades 3-5).

Infections:

Infections and Infestations by SOC were seen in 72.0% in the obinutuzumab arm and 61.7% in the placebo arm. The corresponding frequencies for Grade 3-5 infections were reported in 11.5% arm versus 9.8%, respectively. Deaths due to infection were reported in 2 patients (1.0%) in the obinutuzumab arm (both COVID-19 pneumonia) and 1 patient (0.5%) in the placebo arm (COVID-19). A warning was

included in Section 4.4 of the SmPC to inform on the risk of infections. Further, the following adverse reactions were included in Section 4.8 of the SmPC:

- frequency very common: upper respiratory tract infection (all grades), COVID-19 (all grades), urinary tract infections (UTI) (all grades) and bronchitis (all grades)
- frequency common: pneumonia (all grades), herpes simplex (all grades), COVID-19 (Grades 3-5), UTI (Grades 3-5) and pneumonia (Grades 3-5).

Neutropenia:

Neutropenic events included the AEs of neutropenia and febrile neutropenia as well as the laboratory measure neutrophil count decreased. The number of patients experiencing 'Neutropenia', as a broad medical concept, was 28 patients (14%) in obinutuzumab arm vs 12 patients (6.2%) in placebo arm. The higher frequency in the obinutuzumab arm compared to placebo was also observed for the serious drug-related neutropenia. As of the data cut, all events of serious drug-related neutropenia had resolved.

The majority of neutropenia and related events resolved/improved spontaneously or with use of granulocyte colony-stimulating factors.

A warning was included in Section 4.4 of the SmPC to inform on the risk of neutropenia. Neutropenia was included as adverse reaction Section 4.8 of the SmPC (frequency very common for all grades, frequency common for grades 3-5).

Other AESIs:

GI perforation occurred in 1 patient (0.5%) in each arm. Steroid treatment is part of the standard therapy for LN. Hence, GI perforation was not considered an adverse reaction for the LN population.

No cases of HBV reactivation or PML have been reported (Week 76 safety analysis). However, PML cases have been reported in patients treated for CLL and FL, hence, in view of the seriousness of this risk, a warning is included in SmPC Section 4.4 to inform on this risk for the LN population. Further, HBV reactivation can occur in patients treated with anti-CD20 antibodies, the warning on infections also includes information on this risk for the LN population.

One patient (0.5%) in the obinutuzumab arm experienced drug-related thrombocytopenia in the Regency study, which was grade 4, and which resolved. There were no signs of an acute onset thrombocytopenia in LN studies as seen with treatment in the haematological setting. It was considered that the acute onset of thrombocytopaenia seen in the oncological indications could be associated with the combination with the other cytotoxic drugs given and also as part of an infusion related reactions, which were more prevalent in the haematological setting. Thus, the CHMP agreed to not include thrombocytopenia as an important potential risk for the LN population in the RMP.

No event of worsening of pre-existing cardiac condition was reported in the Regency study. Further, 4 of the 16 patients with a medical history of cardiac disorders reported infusion related reactions; however, none of the patients reported any cardiac symptoms during IRRs. The MAH stated that there is no direct cardiac toxicity with obinutuzumab expected and that fluid overload, infection or IRR may contribute to the events seen in the haemato-oncological population. In addition, the type of pre-existing cardiac conditions could differ between the haemato-oncological and LN population, with serositis such as pleuropericarditis/pericarditis being a manifestation of SLE. Overall, the CHMP concluded that there is insufficient information regarding worsening of cardiac condition at this timepoint to include this as an important potential risk for the LN indication in the RMP. Further, patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period as stated in SmPC Section 4.4 (warning on IRRs for patients with LN).

The frequencies of patients with laboratory abnormalities in chemistry parameters were generally comparable between the obinutuzumab and placebo arms. One exception was a marked difference in IgM with 41% experiencing low IgM in the obinutuzumab arm whereas this was only observed in 13.7% in the placebo arm. Hence, upon the CHMP's request, blood immunoglobulin M decreased (all grades) at the frequency very common was added as adverse reaction in Section 4.8 of the SmPC.

No subgroup analysis for age was considered relevant as there was only one patient >65 years. Stratification analyses indicated a comparable safety profile between Black vs. Other race patients and between regions (USA/Canada vs Latin America and the Caribbean vs. Other). However, only approximately 11% were Black, hence no conclusion could be drawn on the stratification for race. This was also the case for region where approximately 13% were from USA/Canada, 61% from Latin America and the Caribbean, and 25% from Other.

The safety of immunisation with live or attenuated viral vaccines following obinutuzumab therapy has not been studied in LN patients. This was reflected in Section 4.4 of the SmPC, further, vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

In addition, a warning was implemented in Section 4.4 of the SmPC recommending to monitor B-cell depletion in case of exposure in utero to obinutuzumab and to postpone vaccinations with live virus vaccines until the infant's B-cell count has recovered.

The proportion of patients with at least one AE leading to discontinuation from blinded obinutuzumab was low in both the obinutuzumab (5.5% of patients) and placebo arms (4.1% of patients). This included four patients in each arm in the SOC Infections and Infestations and two patients in the obinutuzumab arm due to the PT neutropenia (0 in the placebo arm). Hence, no concern was raised.

The CHMP acknowledged the multi organ involvement of patients with LN since the majority of the patients present other manifestations of SLE, hence, these patients may also be more vulnerable to long term B-cell depletion than the oncology patients. It was also acknowledged that further long-term safety concerns such as malignancies, infections related to prolonged hypoglobulinemia, PML, CVD would need to be further evaluated. Hence, considering the potential long-term use of obinutuzumab in LN patients in addition to the use in combination with MMF also in a maintenance setting, long term safety in LN was included in the RMP as missing information. The long-term part of the Regency study was included as a category 3 study in the RMP.

2.5.2. Conclusions on clinical safety

Risks associated with treatment with obinutuzumab in patients with LN based on the pooled Week 76 safety analysis were mainly infections, neutropenia, and IRRs, which are consistent with those observed in the haematological indications. Blood immunoglobulin M decreased was identified as a new adverse reaction (frequency very common). Long term safety in LN was included in the RMP as missing information. The long-term part of the Regency study was included as a category 3 study in the RMP.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 11.2 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 11.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 11.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Infusion related reactions (all indications) • Infections (all indications) • Thrombocytopenia (oncology indications only) • Worsening of pre-existing cardiac conditions (oncology indications only)
Important potential risks	• Second malignancies (oncology indications only)
Missing information	• Long-term safety (lupus nephritis indication only)

Pharmacovigilance plan

Study title/ Status	**Summary of Objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None	None	None	None	
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None	None	None	None	
Category 3 - Required additional pharmacovigilance activities				
Study CA41705 (REGENCY): A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter	The safety objective for this study is to evaluate the safety of obinutuzumab (combined treatment groups) compared with placebo on the basis of the following	Long-term safety (lupus nephritis indication only)	First patient enrolled 5 August 2020	NA

Study to Evaluate the Efficacy and Safety of Obinutuzumab in Patients with ISN/RPS 2003 Class III or IV Lupus Nephritis	endpoints: • Incidence and severity of adverse events, 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, including, among others, IRRs, neutropenia, infections, and thrombocytopenia • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results These assessments will continue to be performed after study unblinding, during the long-term extension study period to monitor the long-term safety of the obinutuzumab arm.		LPLV	28 February 2031 (8 years after LPI which was 28 February 2023)
			Final Database lock planned	21 March 2031
			Final Clinical Study Report planned	20 March 2032

IRR=infusion-related reaction; ISN/RPS=International Society of Nephrology/Renal Pathology Society; LPLV=last patient last visit; NCI CTCAE=NCI National Cancer Institute Common Terminology Criteria for Adverse Events.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion related reactions (all indications)	**Routine risk communication:** Section 4.2 of the EU SmPC: Posology and method of administration Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	Routine risk minimization activities recommending specific clinical measures to address the risk: Corticosteroid premedication is recommended for patients with FL and mandatory for CLL patients in the first cycle. Premedication to reduce the risk of infusion related reactions. Hypotension, as a symptom of IRRs, may occur during	
	Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro infusion and for the first hour after administration. Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Refer to section 4.4 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None	
Infections (all indications)	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

	Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Gazyvaro should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyvaro	**Additional pharmacovigilance activities:** None
	in patients with a history of recurring or chronic infections. Refer to section 4.4 and 4.8 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None	
Thrombocytopenia (oncology indications only)	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	Refer to section 4.4 and 4.8 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine	
	Additional risk minimization measures: None	
Worsening of pre-existing cardiac conditions (oncology indications only)	**Routine risk communication:** Section 4.4 of the SmPC- Special warnings and precautions for use Section 4.8 of the SmPC- Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution in order to prevent a potential fluid overload. Refer to Section 4.4 and 4.8 of the SmPC for detailed information **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Second malignancies (oncology indications only)	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None	
Long-term safety (lupus nephritis indication only)	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Inclusion in the Periodic Safety Update Report (PSUR/PBRER) with specific discussion on any events related to long-term use **Additional pharmacovigilance activities:** Ongoing long-term extension study: Study CA41705 (REGENCY)

CLL=chronic lymphocytic leukemia, EU=European union; FL=follicular leukemia,
GCSF=granulocyte-colony stimulating factors; IRR=infusion related reaction, SmPC=Summary of product characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

SLE is an autoimmune rheumatic disease that occurs primarily in women of childbearing age. LN is the most common organ-threatening manifestation of SLE and remains a major cause of morbidity and mortality among patients with SLE (Maria and Davidson 2020[1]; Mok et al. 2023[2]; Siegel and Sammaritano 2024[3]; Anders et al. 2020[4]).

Proteinuria is the most common clinical feature of LN and may be accompanied by haematuria, hypertension, volume overload, metabolic abnormalities, and progressive impairment of renal function. The presence of kidney biopsy-proven proliferative nephritis, defined as ISN/RPS 2003 Class III or IV lupus nephritis, is associated with a high risk of progression to ESKD, even with treatment (Hanly et al. 2016[31]; Contreras et al. 2004[5]; Anders et al. 2020[4]).

B cells play a key role in LN and serve multiple functions in the disease pathogenesis through autoantibodies, immune complexes, and amplifying activation of adaptive immune responses (Atisha-Fregoso et al. 2021[32]; Mohan et al. 2015[15]; Foster 2007[33]).

3.1.2. Available therapies and unmet medical need

The primary goal for treating patients with active LN is to stop the active disease process in order to provide long-term preservation of kidney function and prevention of the progression of chronic kidney disease and eventual ESKD. An additional objective is to minimize glucocorticoid use as well as toxicities associated with established therapeutic interventions (Anders et al. 2020[4]; Mohan et al. 2023[15]; Kidney Disease: Improving Global Outcomes [KDIGO] 202416[16]; Hahn et al. 2012[17]).

For several decades, the standard of care therapy for patients with proliferative LN was limited to corticosteroids in combination with either MMF or CYC, along with antimalarials and blood pressure control with RAAS inhibitors (Fanouriakis et al. 2019[18], Hahn et al. 2012[17], Bertsias et al. 2012[19]). MMF, CYC and AZA are standard of care therapies for patients with LN in Europe, but not authorised for this indication; however, they are recommended by the KDIGO 2024 Clinical Practice Guideline for the Management of LN. Unfortunately, these established therapies (corticosteroids in combination with either MMF, CYC or AZA) are associated with substantial toxicities that contribute to the morbidity associated with LN (Hunnicutt et al. 2023[34]; KDIGO 2024[16]).

Recently, a BLyS-specific inhibitor, and a second-generation CNI immunosuppressant, were approved for the treatment of patients with active LN and are recommended treatments for active LN by the KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis.

Despite the use of these new therapies, only a minority of patients achieve a CRR within the first 1–2 years, and the rate of progression to ESKD has not decreased in recent decades (Kale et al. 2023[20]; Mok et al. 2023[2]; Anders et al. 2020[4]).

Overall, there remains a need for safe and effective therapies for the treatment of active LN.

3.1.3. Main clinical studies

The application was based on two clinical studies: the pivotal ongoing Phase III REGENCY study and the supportive completed Phase II NOBILITY study:

REGENCY

This was a pivotal Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluating the efficacy and safety of obinutuzumab versus placebo in patients with Class III or IV LN, with or without concomitant Class V. The study was ongoing at the time of submission. Patients were

[31] Hanly JG, O'Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology. 2016;55(2):252-62.
[32] Atisha-Fregoso Y, Toz B, Diamond B. Meant to B: B cells as a therapeutic target in systemic lupus erythematosus. J Clin Invest. 2021 Jun 15;131(12):e149095. doi: 10.1172/JCI149095. PMID: 34128474; PMCID: PMC8203443.
[33] Foster MH. T cells and B cells in lupus nephritis. Semin Nephrol 2007;27:47-58.
[34] Hunnicutt JN, Georgiou ME, Ma L, Levy RA, Gairy K. Real-World Immunosuppressant Treatment Patterns for Patients with Lupus Nephritis in the United States. Rheumatol Ther. 2023;10(5):1305-1318.

randomized 1:1 to receive obinutuzumab (flat dose of 1000 mg IV) or placebo on top of standard of care (MMF and corticosteroids with a tapering schedule). The obinutuzumab arm was then randomised 1:1 again to receive either a "2-2-2-regimen" (obinutuzumab at Week 1+2, 24+26 and 50+52) or a "2-2-1-regimen" (obinutuzumab at Week 1+2, 24+26 and 52, placebo at Week 50). From Week 76, patients could either 1) continue blinded infusions of obinutuzumab or placebo if exhibiting an adequate response until study unblinding, 2) in case of inadequate response, transfer to open-label treatment with obinutuzumab (on a 2-2-1-regimen) or 3) enter SFU for at least 12 months from the last dose of obinutuzumab/placebo.

The primary efficacy endpoint was a composite endpoint at Week 76 defined as "Proportion of patients who achieved a CRR, with CRR defined as achievement of all of the followings: 24-hour UPCR < 0.5 g/g, eGFR ≥ 85% of baseline, no occurrence of the following intercurrent events: rescue therapy, treatment failure, death, or early study withdrawal".

The key secondary efficacy endpoints were: CRR at Week 76 with successful prednisolone taper to maximum 7.5 mg/day, proteinuric response at Week 76, change in eGFR from baseline to Week 76, death or renal-related events to Week 76, ORR at Week 50 and change in FACIT-F scale from baseline to Week 76.

A total of 271 patients were included in the study: 135 in the obinutuzumab arm (2-2-2 Regimen = 69; 2-2-1 Regimen = 66) and 136 in the placebo arm.

NOBILITY

This was a completed Phase II, randomized, double-blind, placebo-controlled, parallel-group, multicenter study that evaluated safety and efficacy of obinutuzumab versus placebo in patients with Class III or IV LN, with or without concomitant Class V. Patients were randomized in a 1:1 ratio to receive either obinutuzumab 1000 mg (flat dose of 1000 mg IV) or placebo on top of standard of care (MMF/ MPA and corticosteroids with a tapering schedule) at Week 1+2, 24 and 26.

The primary endpoint was a composite endpoint at Week 52, defined as "Proportion of patients who achieved a CRR, with CRR defined as achievement of all of the following: normalization of serum creatinine (Serum creatinine ≤ the ULN range of central laboratory values if the baseline (Day 1) serum creatinine is above the ULN, serum creatinine ≤15% above baseline and ≤the ULN range of central laboratory values if baseline (Day 1) serum creatinine is ≤ the ULN range of central laboratory values), inactive urinary sediment, as evidenced by <10 red blood cells/high power field and the absence of red cell casts, Urinary protein to creatinine ratio (UPCR) <0.5."

A total of 125 patients were included in the study: 63 in obinutuzumab arm and 62 in placebo arm. The study was not powered to provide confirmatory results.

3.2. Favourable effects

In the pivotal Regency study, the primary endpoint of CRR at Week 76 was met with an adjusted difference in proportions of 13.40% (95% CI 1.95, 24.84) based on 46.4% (95% CI 37.95, 54.86) responders in the obinutuzumab arm and 33.1% (95% CI 25.18, 41.00) in the placebo arm. Sensitivity and supplementary analyses of the primary endpoint supported the findings of the primary analysis. The treatment benefit of obinutuzumab was seen across LN disease characteristics and severity (LN class III vs IV, concomitant LN class V, level of UPCR).

The key secondary endpoints were tested hierarchically to adjust for multiplicity. Both the key secondary endpoints at Week 76 of CRR with successful prednisolone taper and proteinuric response were met, i.e., CRR with successful prednisolone taper of max 7.5 mg/day from Week 64-76: 43% vs 31% responders in

obinutuzumab vs placebo arm and an adjusted difference of 11.88% (95% CI: 0.57, 23.18), and proteinuric response defined as UPCR <0.8 g/g and no ICEs defined as in the primary endpoint: 56% vs 42% responders in obinutuzumab vs placebo arm and an adjusted difference of 13.68% (95% CI: 2.01, 25.36).

The key secondary endpoint of mean change in eGFR from baseline to Week 76 was not met (adjusted mean of 2.31 vs -1.54 in obinutuzumab vs placebo arm, giving a difference in adjusted means of 3.8, 95% CI: -1.8, 9.5). The statistical significance of subsequent endpoints was automatically rejected.

The SLE-related laboratory endpoints (supportive secondary endpoints) showed generally greater reduction in anti-dsDNA titers and greater increase of C3, from baseline to Week 50. Changes in SLEDAI-2K score from baseline to Week 76 were similar between the obinutuzumab and placebo arm. The CHMP concluded that the available data do not indicate that obinutuzumab has deleterious effects on other organs that would offset the benefit on renal function.

An additional dose was given at Week 50 for the 2-2-2 regimen compared to the 2-2-1 regimen. Descriptive analysis of the 2 regimens for the primary secondary endpoints indicated comparable point estimates of responder rates in both obinutuzumab arms at Week 76. The CHMP acknowledged that the time period of 24 weeks for evaluation of differences between the 2 regimens was too short. Further, logistic regression analysis based on AUC0-76 indicated that the difference in CRR occurrence (~4%) at Week 76 was minor. The proposed 2-2-1 dosing of obinutuzumab and at every 6 months from Week 52 was endorsed by the CHMP.

The supportive Nobility study assessed a primary endpoint of CRR at Week 52 defined differently than in the Regency study, but incorporating the same level of proteinuria (<0.5 g/g) with additional criteria of urinary sediment to assess (lack of) activity and renal function was assessed by serum creatinine rather than eGFR. The study was not powered to provide confirmatory results. The primary endpoint was met by numerically more patients in the obinutuzumab arm (n=22, 35%) compared to the placebo arm (n=14, 23%) and the findings were considered supportive of the findings in the Regency study.

3.3. Uncertainties and limitations about favourable effects

There were uncertainties regarding the long-term effect on renal function since the secondary key endpoint of mean change in eGFR from baseline to Week 76 was not met. Response rates beyond week 76 for all included patients and for patients deemed adequate responders at week 76 appeared to support that a substantial proportion of adequate responders at week 76 maintain CRR on blinded obinutuzumab infusions. However, the CHMP acknowledged the small sample size of patients continuing blinded obinutuzumab treatment beyond Week 76. Hence, SmPC Section 4.2 was updated to indicate that 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.

For the very small group of patients with an eGFR of 30-60 mL/min/1.73 m2 (n=31), the efficacy in both the placebo and obinutuzumab group appeared negative (responders obinutuzumab: 16.7%, responders placebo: 26.3%). Similarly, the treatment effect was low or close to zero in patients with a prior history of LN. The lacking or reduced efficacy in patients with eGFR between 30 and 60 or a prior history of LN may be explained by the fact that these patients may be unlikely to achieve a proteinuric response due to chronic kidney disease/proteinuria. Hence, the CHMP acknowledged the remaining uncertainty regarding the treatment efficacy in these patients and did not further pursue the issue.

There was an imbalanced Hispanic representation across treatment arms (52.6% in the obinutuzumab group, 62.5% in the placebo group). Post hoc subgroup analyses of CRR of the subgroup Hispanic Y/N showed a generally consistent treatment benefit in favour of obinutuzumab across the subgroups.

However, given the limited sample size and the *post hoc* nature of the analyses, no firm conclusion could be drawn. The CHMP considered that it cannot be fully ruled out that the main positive outcome for obinutuzumab in Regency study is in fact a result of confounding from uneven randomization of Hispanic patients. The CHMP concluded that the risk was sufficiently low and the issue was not further pursued.

3.4. Unfavourable effects

IRRs were reported in 13.5% of patients in the obinutuzumab arm vs 10.4% of patients in the placebo arm. Most were Grade 1-2 events, and all Grade 3-4 IRRs occurred in conjunction with either the first or second infusion; 3/200 in the obinutuzumab arm and 1/193 in the placebo arm. A warning was included in the SmPC Section 4.4 to inform on the risk of IRR. SmPC Section 4.2 includes information on the management of IRR. Further, IRR were included as adverse reactions in Section 4.8 of the SmPC (frequency very common for all grades, frequency common for grades 3-5).

Infections and Infestations by SOC were seen in 72.0% in the obinutuzumab arm and 61.7% in the placebo arm. The corresponding frequencies for Grade 3-5 infections were reported in 11.5% arm vs 9.8%, respectively. Deaths due to infection were reported in 2 patients (1.0%) in the obinutuzumab arm (both COVID-19 pneumonia) and 1 patient (0.5%) in the placebo arm (COVID-19). A warning was included in Section 4.4 of the SmPC to inform on the risk of infections. Further, the following adverse reactions were included in Section 4.8 of the SmPC:

- frequency very common: upper respiratory tract infection (all grades), COVID-19 (all grades), urinary tract infections (UTI) (all grades) and bronchitis (all grades)
- frequency common: pneumonia (all grades), herpes simplex (all grades), COVID-19 (Grades 3-5), UTI (Grades 3-5) and pneumonia (Grades 3-5).

Neutropenic events included the AEs of neutropenia and febrile neutropenia as well as the laboratory measure neutrophil count decreased. The frequency of neutropenia was higher in the obinutuzumab arm (20 patients; 10.0%) compared to the placebo arm (7 patients; 3.6%). The higher frequency in the obinutuzumab arm compared to placebo was also observed for the serious drug-related neutropenia. A warning was included in Section 4.4 of the SmPC to inform on the risk of neutropenia. Neutropenia was included as adverse reaction Section 4.8 of the SmPC (frequency very common for all grades, frequency common for grades 3-5).

Laboratory values collected as part of routine laboratory monitoring in clinical studies showed that there was a marked difference in IgM with 41% experiencing low IgM in the obinutuzumab arm compared to 13.7% in the placebo arm. Blood IgM decreased was therefore added as adverse reaction in the Section 4.8 of the SmPC (frequency very common). This is a reaction that was not previously reported in the oncological indications.

No cases of HBV reactivation or PML have been reported in LN patients. However, PML cases have been reported in patients treated for CLL and FL, hence, in view of the seriousness of this risk, a warning was included in SmPC Section 4.4 to inform on this risk for the LN population. Further, HBV reactivation can occur in patients treated with anti-CD20 antibodies, hence, a warning was included in SmPC Section 4.4 to inform on this risk for the LN population.

3.5. Uncertainties and limitations about unfavourable effects

The long-term effect of the lymphocyte-depletion by obinutuzumab in LN patients treated with standard of care therapy (immunomodulating agents) could potentially add to the risk of serious infections. Hence, considering the potential long-term use of obinutuzumab in LN patients in addition to the use in

combination with MMF also in a maintenance setting, long term safety in LN was included in the RMP as missing information. The long-term part of the REGENCY study was included as a category 3 study in the RMP.

3.6. Effects Table

Table 66 Effects Table for Gazyvaro for active LN.

Effect	Short description	Unit	Treatment Gaz.+std.	Control Pcb.+std.	Uncertainties / Strength of evidence	References
Favourable Effects[1]			**n=135**	**n=136**		
CRR at Week 76	Meeting all criteria: UPCR < 0.5 g/g ; eGFR ≥ 85% of baseline; no occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal	N (%)	60 (46.4)	45 (33.1)	Treatment difference: 13.40 (95% CI 1.95, 24.84) p-value: 0.0232	REGENCY study
CRR with successful prednisone taper at Week 76	No receipt of prednisone > 7.5 mg/day from Week 64-Week 76	N (%)	55 (42.7)	42 (30.9)	Treatment difference: 11.88 (95% CI 0.57, 23.18) p-value: 0.0421	REGENCY study
Proteinuric response at Week 76	Meeting all criteria: UPCR < 0.8 g/g ; no occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal	N (%)	72 (55.5)	56 (41.9)	Treatment difference: 13.68 (95% CI (2.01, 25.36) p-value: 0.0227	REGENCY study
Unfavourable Effects[2]			**n=200**	**n=193**		
Adverse events	All Grade 3-5 Serious AEs	N (%)	183 (91.5) 62 (31.0) 57 (28.5)	171 (88.6) 38 (19.7) 39 (20.2)		Pooled Week 76 population
	Deaths	N (%)	4 (2.0)	3 (1.6)		Pooled Week 76 population
Infections (SOC)	All Grade 3-5	N (%)	144 (72.0) 22 (11.0)	119 (61.7) 19 (9.8)		Pooled Week 76 population

Effect	Short description	Unit	Treatment Gaz.+std.	Control Pcb.+std.	Uncertainties / Strength of evidence	References
Neutropenia*	All	N (%)	28 (14.0)	12 (6.2)		Pooled Week 76 population
IRR*	All	N (%)	27 (13.5)	20 (10.4)		Pooled Week 76 population
Low Immunoglobulin M	Based on laboratory value	N(%)	66** (41.3)	22** (13.7)		Week 76 safety analysis

Abbreviations: CRR: Complete Renal Response; Gaz.: Gazyvaro, IRR: infusion-related reactions, Pcb: placebo; UPCR: urine protein-creatinine ratio;

Notes: [1]Based on the main study Regency, [2]Pooled safety data from Regency and Nobility studies up until week 76

*Pooled term, according to methodology used for adverse drug reaction determination

** Values available for 160 patients in obinutuzumab arm and 161 patients in placebo arm

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal Phase III study Regency assessed a composite primary outcome of CRR, including both reduction of proteinuria and preservation of eGFR, at Week 76 was met. This endpoint was considered by the CHMP a clinically relevant measurement. The key secondary endpoints of CRR with a successful steroid tapering (max 7.5 mg/day from Week 64-76), and obtainment of proteinuric response (UPCR <0.8g/g) were also statistically clinically relevant.

In this study, patients received either obinutuzumab and MMF (obinutuzumab arm), or placebo and MMF (placebo arm) and a tapering course of corticosteroids in both treatment arms. The study showed that obinutuzumab resulted in a higher proportion of patients obtaining the primary outcome of CRR at Week 76 compared to placebo. The treatment benefit of obinutuzumab was seen across LN disease characteristics and severity. Also, the proportion of patients obtaining the key secondary endpoints of CRR with successful steroid taper and proteinuric response were higher in the obinutuzumab arm compared to placebo. The key secondary endpoint of mean change in eGFR was not met but showed in favour of the obinutuzumab arm. As the other key secondary endpoints were tested hierarchically for multiplicity, this resulted in automatic rejection of the subsequent endpoints. The SLE-related laboratory endpoints (anti-dsDNA titers, C3 and SLEDAI-2K) indicated that obinutuzumab is not expected to have deleterious effects on other organs that would offset the benefit on renal function.

The MAH initially applied for the following indication: *for the treatment of adult patients with active lupus nephritis who are receiving standard therapy*. However, obinutuzumab was studied in patients with active class III and IV LN with/without concomitant class V LN, and in combination with MMF. Hence, the indication was revised in accordance with the studied population and the combination therapy as follows: *"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)"*.

The EMA Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2013) states that a two-year period for assessing outcomes is needed for an agent used both as induction and maintenance. However, information on

obinutuzumab treatment beyond Week 76 were limited to the adequate responders at Week 76 who continued blinded obinutuzumab and placebo infusions. A substantial proportion of adequate responders at week 76 maintained CRR on blinded obinutuzumab infusions. The CHMP acknowledged the limited sample size. Hence, SmPC Section 4.2 was updated to indicate that 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. Final results from the Regency study are expected to be provided by March 2032 and will inform further on the longer-term efficacy in patients with LN.

The risks associated with obinutuzumab treatment in patients with LN based on the pooled Week 76 safety analysis were mainly infections, neutropenia, and IRRs, which were consistent with those observed in the haematological setting. *Blood immunoglobulin M decreased* was a new adverse reaction observed in LN studies but not previously identified in the haematological setting. Long-term safety data were limited and the long-term effect of the lymphocyte-depletion by obinutuzumab in LN patients treated with standard of care therapy in the form of immunomodulating agents (steroids and MMF) could potentially add to the risk of serious infections. Hence, long term safety in LN patients was included in the RMP as missing information. The long-term part of the Regency study was included as a category 3 study in the RMP.

3.7.2. Balance of benefits and risks

The results from the pivotal Regency study showed a statistically significant and clinically relevant effect on renal parameters for obinutuzumab in combination with MMF and corticosteroid in adult patients with Class III and IV LN with and without Class V LN. This response was demonstrated across LN class and severity of proteinuria. No deleterious effects were observed on other organs that would offset the benefit on renal function.

The safety profile of obinutuzumab was already characterised in the haematological setting and besides decreased *blood immunoglobulin M,* no new safety concerns were identified. Long term safety in LN patients was included in the RMP as missing information and is expected to be further characterised following completion of the long-term part of the REGENCY study. Overall, the safety profile of obinutuzumab was in line with previous observations and was outweighed by the benefits observed in patients with LN.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit risk of Gazyvaro is positive in the following indication: *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)*

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following

change:

Variation accepted		Type	Annexes affected
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB

Extension of indication to include for Gazyvaro, in combination with mycophenolate mofetil (MMF), the treatment of adult patients with active Class III or IV, with or without concomitant Class V, lupus nephritis (LN), based on results from study Regency (CA41705). This is an ongoing, Phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of obinutuzumab administered at standard infusion rates in patients with ISN/RPS 2003 Class III or IV lupus nephritis treated with standard-of-care therapy (MMF and corticosteroids with a tapering schedule).

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated.

The Package Leaflet is updated in accordance. Version 11.2 of the RMP is approved.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Gazyvaro-H-C- 002799-II- VR/0000244907'