25 March 2021
EMA/CHMP/548269/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Benlysta

International non-proprietary name: belimumab

Procedure No. EMEA/H/C/002015/II/0080

Note

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

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List of abbreviations

AE	Adverse Event
AESI	Adverse events of special interest
ADA	Anti-drug antibody
Anti-dsDNA	Anti-double stranded deoxyribonucleic acid
AZA	Azathioprine
Cavg	Steady-state average concentration
CI	Confidence interval
CRR	Complete renal response
CSR	Clinical study report
CYC	Cyclophosphamide
eGFR	Estimated glomerular filtration rate
E-R	Exposure-response
ESRD	End-stage renal disease
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HDCS	High dose corticosteroids
HR	Hazard ratio
HZ	Herpes zoster
Ig	Immunoglobulin
IP	Investigational product
IPD/TF/WD=NR	Investigational Product Discontinuation/Treatment Failures/Study Withdrawal=Non-Responder
ISN	International Society of Nephrology Working Group
IV	Intravenous, intravenously
kg	Kilogram
LN	Lupus nephritis
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
mg	Milligram
MMF	Mycophenolate mofetil
mITT	Modified Intention-to-Treat
mL	Milliliter

MPA	Medicines Products Agency
OI	Opportunistic infections
OR	Odds ratio
ORR	Ordinal response rate
PERR	Primary efficacy renal response
PMC	Post-Marketing Commitment
PML	Progressive multifocal leukoencephalopathy
q2w	Every 2 weeks
q4w	Every 4 weeks
qw	Weekly
RAP	Reporting and Analysis Plan
RPS	Renal Pathology Society Working Group
S2K	SLEDAI-2K
SAE	Serious adverse event
SC	Subcutaneous(ly)
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SOC	System organ class
SLEDAI-S2K	SELENA SLEDAI with modified SLEDAI-2K scoring for proteinuria
TB	Tuberculosis
TF	Treatment failure
uPCR	Urine protein to creatinine ratio

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline (Ireland) Limited submitted to the European Medicines Agency on 24 June 2020 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of lupus nephritis for belimumab; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 39 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0183/2016 and P/0003/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0003/2020 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 did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: <N/A>

Timetable	Actual dates
Submission date	24 June 2020
Start of procedure:	18 July 2020
CHMP Rapporteur Assessment Report	11 September 2020
PRAC Rapporteur Assessment Report	11 September2020
PRAC members comments	23 September 2020
Updated PRAC Rapporteur Assessment Report	24 September 2020
PRAC outcome	01 October 2020
CHMP members comments	05 October 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	08 October 2020
Request for supplementary information	15 October 2020
Submission of MAH responses	27 November 2020
Re-start of procedure	28 November 2020
CHMP Rapporteur Assessment Report	22 December 2020
PRAC Rapporteur Assessment Report	04 January 2021
PRAC members comments	06 January 2021
Updated PRAC Rapporteur Assessment Report	07 January 2021
PRAC Outcome	14 January 2021
CHMP members comments	18 January 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 January 2021
Request for supplementary information	28 January 2021
Submission of MAH responses	23 February 2021
Re-start of procedure	24 February 2021
PRAC Rapporteur Assessment Report	1 March 2021
PRAC members comments	3 March 2021
Updated PRAC Rapporteur Assessment Report	4 March 2021
CHMP Rapporteur Assessment Report	10 March 2021
PRAC outcome	11 March 2021
CHMP members comments	15 March 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 March 2021
Opinion	25 March 2021

2. Scientific discussion

2.1. Introduction

The marketing authorisation approval of belimumab (Benlysta) for treatment of systemic lupus erythematosus (SLE) in 2011 was based on clinical trials in subjects with active SLE receiving standard therapy. Due to the differences in treatment and efficacy measures between SLE and lupus nephritis (LN), subjects with severe active renal lupus were excluded from these trials. The MAH has since conducted BEL114054, a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of intravenous (IV) belimumab plus standard therapy compared to placebo plus standard therapy for induction and maintenance of renal response and prevention of renal worsening in adult subjects with active LN over a 2-year treatment period. This study was a Post-Marketing Commitment (PMC) to the US Food and Drug Administration (FDA) and a Category 3 Study in the EU RMP.

In this variation application, the MAH sought initially to include the following therapeutic indication:

- *treatment of lupus nephritis in adult patients who are receiving standard therapy.*

The proposed posology in Section 4.2 of the SmpC was:

- Subcutaneous dosing: 400 mg dose (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. In patients not requiring induction therapy for lupus nephritis, the recommended dosage is 200 mg once weekly

- Intravenous dosing: 10 mg/kg Benlysta on Days 0, 14 and 28, and at 4 week intervals thereafter.

- Transition from IV to SC administration: first subcutaneous injection could be proposed 1 to 2 weeks after the last intravenous dose. The transition could occur any time after the patient completes the first 2 intravenous doses.

2.1.1. Problem statement

Disease or condition

SLE is a heterogeneous chronic autoimmune inflammatory disease. A complex interplay between abnormally activated B and T cells, antigen presenting cells, and the complement system results in a multisystem injury, including kidneys [Anders, 2016[1]; Menez, 2018[2]; Lech, 2013[3]; Edelbauer, 2011[4]].

Renal involvement is present in an average of 38% of patients at the time of SLE diagnosis and occurs in 40-70% of SLE patients during the course of their disease. SLE patients that are more likely to develop renal disease are typically of younger age, are male and are African, Asian or Hispanic. Approximately 10-20% of patients progress to ESRD within 10-15 years since LN diagnosis. LN is the most common and

[1] Anders HJ, Rovin B.A pathophysiology-based approach to the diagnosis and treatment of lupus nephritis. Kidney Int. 2016;90(3):493-501.
[2] Menez SP, El Essawy B, Atta MG. Lupus Nephritis: Current Treatment Paradigm and Unmet Needs. Rev Recent Clin Trials. 2018;13(2):105-13.
[3] Lech M, Anders HJ. The pathogenesis of lupus nephritis. J Am Soc Nephrol. 2013;24(9):1357-66.
[4] Edelbauer M, Ho J. Molecular evaluation of renal biopsies: a search for predictive and prognostic markers in lupus nephritis. Expert Rev Mol Diagn. 2011;11(6):561-5.

severe systemic manifestation of SLE that remains the most significant cause of morbidity and mortality [Hanly, 2016**Error! Bookmark not defined.**; Menez, 2018[2]; Anders, 2020[5]].

LN is an immune complex mediated glomerulonephritis. Intra-renal pathogenesis of LN includes antibody binding to multiple intrarenal autoantigens, tertiary lymphoid tissue formation with local antibody production and complement activation resulting in complement-mediated damage, and release of cytokines associated with cellular proliferation and matrix formation. Elevated serum and intra-renal levels of B-lymphocyte stimulator (BLyS) play an important role in development and perpetuation of renal inflammation cycle [Lech, 2013[3]; Liu, 2014[6]; Kang, 2017[7]].

The location of immune complex deposition as confirmed by renal biopsy, defines the different histopathological classes of LN according to the Renal Pathology Society Working Group and the International Society of Nephrology Working Group (ISN/RPS Criteria from 2003) classification and informs the LN management and prognosis.

LN manifestations range from minimal proteinuria and microscopic hematuria to nephrotic range proteinuria, urinary casts, severe hypertension, peripheral edema, and renal insufficiency or acute renal failure. Typical disease course of LN is characterized by episodes of flares interspersed between periods of disease quiescence [Yap, 2018[8]]. The proportion of LN patients experiencing a flare will vary depending on LN stage, therapies used and adherence to said therapies [Haji, 2017[9]]. Each LN flare and poorly controlled renal disease activity between the flares result in accumulating nephron loss and progressive decline in renal function decades before the end of normal life span, making LN a major risk factor for progression to ESRD and mortality in SLE [Anders, 2016[1]]. In a recent review of a large inception SLE cohort, patients had significantly higher risks of developing ESRD (HR: 44.7, 95% CI: 6.1-329.7) and death (HR: 3.2, 95% CI: 1.6-6.5) after being diagnosed with LN [Hanly, 2016[10]; Almaani, 2017[11]; Menez, 2018[2]].

Mortality is highest amongst SLE patients with proliferative renal involvement (Classes III and IV) and progression to renal failure is strongly predictive of mortality. This poor prognosis is related to risk associated with the development of chronic renal disease, as well as manifestations of more severe forms of systemic disease and cardiovascular complications [Anders, 2016[1]; Almaani, 201711]. Pure membranous LN (Class V) is a less common form of LN, but some studies have found that its impact is almost as high as diffuse proliferative LN [Vachvanichsanong, 2009[12]]. It has been reported that in approximately 40% of patients with pure Class V LN, it eventually transformed to proliferative LN [Narvaez, 2017[13]].

[5] Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nat Rev Dis Primers. 2020;6(1):7. doi: 10.1038/s41572-019-0141-9.
[6] Liu Y, Anders HJ. Lupus nephritis: from pathogenesis to targets for biologic treatment. Nephron Clin Pract. 2014;128(3-4):224-31.
[7] Kang S, Fedoriw Y, Brenneman EK, Truong YK, Kikly K, Vilen BJ. BAFF Induces Tertiary Lymphoid Structures and Positions T Cells within the Glomeruli during Lupus Nephritis. *J Immunol.* 2017;198(7):2602-2611.
[8] Yap DY, Yung S, Chan TM. Lupus nephritis: An update on treatments and pathogenesis. Nephrology (Carlton). 2018;23 (Suppl 4):80-3.
[9] Hajji M, Harzallah A, Kaaroud H, Barbouch S, Hamida FB, Abdallah TB. Factors associated with relapse of lupus nephritis: A single center study of 249 cases. Saudi J Kidney Dis Transpl. 2017;28(6):1349-55.
[10] Hanly JG, O'Keeffe AG2 Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology (Oxford). 2016;55(2):252-62.
[11] Almaani S, Meara A, Rovin RH. Update on Lupus Nephritis. Clin J Am Soc Nephrol 2017;12:825–835.
[12] Vachvanichsanong P, McNeil E. Diffuse proliferative glomerulonephritis does not determine the worst outcome in childhood-onset lupus nephritis: a 23-year experience in a single centre. Nephrol Dial Transplant. 2009:24(9):2729-34.
[13] Narvaez J, Ricse M, Goma M, Mitjavila F, Fulladosa X, Capdevila O, et al.The value of repeat biopsy in lupus nephritis flares. Medicine (Baltimore). 2017; 96(24): e7099.

Clinical management

At present, there are no (e.g., US) or limited (e.g., UK, cyclophosphamide/corticosteroid) approved treatment options for LN. Current approaches to the management of LN continue to rely on high dose corticosteroids (HDCS) and broad-spectrum immunosuppressive agents. First line standard therapies include CYC and HDCS for induction followed by AZA for maintenance or MMF and HDCS for induction followed by MMF for maintenance [Appel, 2009[14]; Dooley, 2011[15]; Houssiau, 2002[16]; Houssiau, 2010[17]; Morris, 2013[18]].

The overarching goal of a long-term LN management strategy is to prevent chronic kidney disease (CKD) and ESRD by aggressively treating acute renal inflammation and minimizing the risk of further renal flares.

The objective of induction therapy in active LN is to rapidly attenuate immune complex mediated inflammation with HDCS and to interrupt the autoimmune pathways with potent immunosuppressants to prevent reignition of the inflammatory cycle. The objective of less intensive but prolonged maintenance therapy is to consolidate the achieved response into a clinical remission and to keep patients relapse-free while minimizing treatment toxicity [Parikh, 2016[19]; Almaani, 201711].

Despite the aggressive nature of treatment, management of LN remains unsatisfactory. More than 60% of patients fail to achieve remission and up to 25% of patients in remission experience relapse. Suboptimal disease control results in irreversible nephron loss and progression to ESRD within 10-15 years of LN diagnosis. In addition to the challenges presented by the severity of the disease, cumulative exposure to potent non-selective immunosuppressants and corticosteroid burden are associated with significant side effects, long-term toxicities and organ damage accrual [Almaani, 2017[2]; Menez, 2018[2]].

A recent meta-analysis of LN outcomes in more than 18000 LN patients over a 40 year period demonstrated that the rates of progression to ESRD and mortality have not changed appreciably in recent years [Tektonidou, 2016[20]]. This pattern further underlines the limitation of current LN therapies and urgent need for new targeted treatments that can optimize outcomes and improve long-term benefit by reducing kidney inflammation, decreasing LN flares, and delaying progression to ESRD.

2.1.2. About the product

Belimumab is a recombinant human IgG1λ monoclonal antibody that binds and antagonizes the biological activity of soluble BLyS [also known as B-cell activating factor (BAFF)] protein, a member of the tumour necrosis factor ligand superfamily that promotes the survival of B lymphocytes. Benlysta is approved for the *treatment of patients with active, autoantibody-positive SLE who are receiving standard therapy* and has been on the market since 2011. Benlysta has been studied in 5 efficacy and safety double-blind randomized controlled trials in adult patients with SLE, and a large double-blind randomized controlled safety trial. In the clinical development programme as of 08 March 2019, 7232 subjects have received treatment with belimumab (IV or SC), and the post marketing exposure is over 83,500 subject-years. In

[14] Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate Mofetil versus Cyclophosphamide for Induction Treatment of Lupus Nephritis. J Am Soc Nephrol. 2009;20:1103–12.
[15] Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al. Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis. N Engl J Med. 2011;365:1886-95.
[16] Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ed Ede R, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum. 2002;46(8):2121-31.
[17] Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis. 2010;69:2083–9.
[18] Morris HK, Canetta PA, Appel GB. Impact of the ALMS and MAINTAIN trials on the management of lupus nephritis. Nephrol Dial Transplant. 2013;28(6):1371-6.
[19] Parikh SV, Rovin BH. Current and Emerging Therapies for Lupus Nephritis. J Am Soc Nephrol. 2016;27(10):2929-2939.
[20] 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. Arthritis Rheumatol. 2016;68(6):1432-41.

2019, belimumab IV formulation was approved for the treatment of children 5 years and older with active autoantibody-positive SLE who are receiving standard therapy.

The belimumab SLE studies excluded subjects with severe active LN because those trials required subjects to be on stable background therapy and had main outcome measures for overall SLE disease activity; patients with active nephritis receive more aggressive background therapy with renal specific assessments required for trial conduct.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No central scientific advice has been sought from the CHMP. The LN study was an agreed post approval commitment with both the EMA and the FDA at the time of the initial MA for Benlysta IV in 2011 and the protocol was submitted to both agencies. Study protocols amendments were assessed as part of variations IB/0030/G and II/0049.

The original agreed study sample size and endpoints were amended after the study initiation. The key changes were communicated to the agencies and are as follows:

- Sample size change from 464 subjects (1:1 Benlysta, placebo allocation) to at least 400 subjects due to difficulties enrolling. The final actual total enrolled was 448 subjects.
- The original primary endpoint definition was changed from an ordinal response rate (ORR) endpoint (complete, partial, no response) to a binary endpoint (responder, non-responder) referred to as PERR. The PERR endpoint is easier to interpret and is clinically relevant as a predictor of long-term renal outcomes. The more stringent endpoint of CRR was included as the first major secondary endpoint in the statistical testing hierarchy.

2.1.4. General comments on compliance with GLP

All studies were undertaken in accordance with standard operating procedures of the GSK Group of Companies, which comply with the principles of GCP. During the conduct of BEL114054, GCP non-compliance was identified at 2 sites; efficacy data from these sites were excluded. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where required, regulatory approval was obtained from the relevant health authority.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Belimumab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no Environmental Risk Assessment for belimumab is required. The CHMP considered this acceptable.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

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

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 community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol No.	No. Study Centers Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)
BEL114054 (Double-blind endpoint analysis)	166 centers in 21 countries across 4 regions: Asia, Europe, US/Canada, Americas excluding US/Canada	Started July 2012 Completed Double-blind Phase July 2019 Enrolled 448/448	To evaluate the efficacy, safety and tolerability of belimumab in adult subjects with lupus nephritis Class III, IV, or V	Phase 3, Randomized; double-blind; placebo-controlled; parallel group	18 years or older in age, active, biopsy-proven proliferative lupus nephritis Class III or IV with or without Class V, or pure Class V membranous, ANA titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL, active renal disease requiring induction therapy with HDCS with either CYC or MMF or oral forms of mycophenolate	Placebo or Belimumab 10 mg/kg; on Days 1, 14, 28, and every 28 days thereafter; IV infusion; 100 weeks	Placebo: 132/223 Belimumab: 146/223	393 F/53 M 33.4 years (18-77)	Primary Efficacy Renal Response at Week 104 (uPCR ≤0.7 and eGFR no more than 20% below pre-flare value or ≥60 mL/min/1.73m² and-Not a Treatment Failure)

ANA = Anti-nuclear antibodies
AZA = Azathioprine
CYC = Cyclophosphamide
eGFR = Estimated glomerular filtration rate
F = Female
HDCS = High dose corticosteroids
IV = Intravenous
M = Male
MMF = Mycophenolate mofetil
uPCR = Urine protein to creatinine ratio

2.3.2. Pharmacokinetics

Introduction

Belimumab PK are consistent with other mAbs targeting soluble ligands. The PK are linear, dose-proportional and time-independent after both IV and SC administration. Belimumab is restricted to the plasma and interstitial fluid of the more permeable tissues and has a small volume of distribution (5.3 L), a clearance (CL) of 215 mL/day, and a 19.4-day terminal half-life [Struemper, 2013[21]]. Belimumab is eliminated by cellular catabolism following non-specific uptake by pinocytosis. In SLE, the geometric mean of the population PK predicted belimumab steady-state Cavg,ss was 100 µg/mL at the

[21] Struemper H, Chen C, Cai, W. Population pharmacokinetics of belimumab following intravenous administration in patients with systemic lupus erythematosus. *J Clin Pharmacol*. 2013;53:711-20.

recommended IV dose of 10 mg/kg q4w and was 102 µg/mL for the recommended SC dose of SC 200 mg qw.

Methods

Bioanalytical methods

There have been no relevant changes to the information presented in the initial marketing authorisation dossier in the treatment of adult SLE for the IV and SC formulations of belimumab.

The immunogenicity methods have been used in previous submissions of Benlysta.

Population Pharmacokinetic Analysis

The population analysis dataset contained data from 448 subjects, 224 randomized to placebo (59 who received cyclophosphamide, CYC, and 165 who received mycophenolate mofetil, MMF, as the induction regimen) and 224 randomized to 10 mg/kg belimumab (60 who received CYC and 164 who received MMF as induction regimen).

The population PK analysis dataset utilized 2156 observed belimumab concentrations from the 224 subjects randomized to belimumab after excluding all pre-first dose records and all records reported as missing or below the limit of quantification. The median number of PK concentrations per subject was 10 with a minimum of 1 and a maximum of 12. During the model fitting process, it was necessary to exclude one PK concentration (57.4 µg/mL on day 728) since this observation occurred approximately 2 years after the last reported belimumab dose and the concentration was not consistent with the 19-day terminal half-life expected for belimumab.

Of the 448 subjects in the overall population PK analysis dataset (Table 1 and Table 2), the majority of patients were female (88%) and approximately half the subjects were Asian. The continuous and categorical covariate distributions at baseline were similar for the belimumab and placebo treatment groups. The median proteinuria level at baseline in the overall study population was 2.5 g/g.

Table 1 Baseline Subject Characteristics by Treatment Arm: Continuous Covariates

Subject Characteristic at Baseline	Median (Min – Max)		
	Overall	Placebo	Belimumab
Age (Years)	31 (18 - 77) (N=448)	31 (18 - 77) (N=224)	31 (18 - 63) (N=224)
Weight (kg)	60.0 (34.0 – 136.9) (N=448)	60.3 (34.0 - 131.2) (N=224)	59.0 (36.9 - 136.9) (N=224)
BMI (kg/m2)	23.1 (14.9 - 51.3) (N=448)	23.1 (14.9 - 51.3) (N=224)	22.9 (16.0 - 45.7) (N=224)
Fat-Free Mass (kg)	38.4 (25.1 - 77.4) (N=448)	38.5 (25.1 - 75.5) (N=224)	38.1 (26.3 - 77.4) (N=224)
Albumin (g/L)	31.0 (14.0 – 43.0) (N=448)	32.0 (14.0 - 43.0) (N=224)	31.0 (16.0 - 42.0) (N=224)
IgG (g/L)	9.1 (1.9 - 48.4) (N=448)	8.8 (1.9 - 42.1) (N=224)	9.5 (2.1 - 48.4) (N=224)
BLyS (ng/mL)	0.48 (0.05 - 10.51) (N=447)	0.49 (0.05 - 5.40) (N=223)	0.48 (0.05 - 10.51) (N=224)
Naïve CD19+CD20+CD27- B Cells (cells/µL)	152 (3 - 1471) (N=406)	151 (3 - 1471) (N=201)	153 (4 - 967) (N=205)
Proteinuria (g/g)	2.50 (0.16 - 35.13) (N=448)	2.47 (0.16 - 35.13) (N=224)	2.61 (0.18 - 16.57) (N=224)
eGFR (mL/min/1.73m2)	99 (14 - 243) (N=448)	98 (22 - 243) (N=224)	99 (14 - 208) (N=224)
SELENA-SLEDAI (score)	12 (4 - 29) (N=447)	12 (4 - 26) (N=223)	12 (4 - 29) (N=224)

Abbreviations: BMI = body mass index; IgG = Immunoglobulin G; BLyS = B-lymphocyte stimulating protein; eGFR = estimated glomerular filtration rate.

Table 2 Baseline Subject Characteristics by Treatment Arm: Categorical Covariates

Subject Characteristic at Baseline	Category	Number (%) of Subjects		
		Overall (N=448)	Placebo (N=224)	Belimumab (N=224)
Induction Regimen	Cyclophosphamide	119 (27%)	59 (26%)	60 (27%)
	Mycophenolate Mofetil	329 (73%)	165 74%)	164 (73%)
Sex	Females	394 (88%)	196 (87.5%)	198 (88%)
	Males	54 (12%)	28 (12.5%)	26 (12%)
Race	American Indian	10 (2%)	6 (3%)	4 (2%)
	Asian	224 (50%)	109 (49%)	115 (51%)
	Black	61 (14%)	31 (14%)	30 (13%)
	Multiple	5 (1%)	3 (1%)	2 (1%)
	White	148 (33%)	75 (33%)	73 (33%)

The population PK model previously developed for an adult SLE population included several covariates on the clearance (CL) and central volume (V1) parameters. Significant covariates on CL included bodyweight, creatinine clearance, proteinuria as a categorical covariate (above or below 2 g/g), angiotensin-converting enzyme inhibitor use, corticosteroid use, albumin and immunoglobulin G (IgG) levels. Significant covariates on V1 included body weight, body mass index (BMI), hemoglobin level and white blood cell count. The adult SLE model was used to evaluate the PK in the adult LN study (BEL114054)

with the population parameters fixed at their adult SLE derived estimates. The results acted as a point of reference to explore the similarities in PK between adult SLE and adult LN patients and to assess how potential improvement in renal function during the study impacts belimumab exposure. The adult SLE model was then reduced to include only the covariates considered essential in characterizing the PK of belimumab in an adult LN population: body weight to capture the allometric effects of body size on clearance and volume of distribution as observed in the previous adult SLE study and proteinuria to capture the renal component of belimumab clearance. The PK model was updated to include fat-free mass instead of body weight to describe the allometric effects of body size in adults with LN, and updated to capture the correlated and time-varying relationship between proteinuria, albumin and belimumab CL. Albumin levels were standardised relative to a theoretically derived value which would be observed in healthy subjects with no proteinuria (estimated to be 42 g/L).

The following covariates were tested in the model development: Age, Sex, Induction regimen, Asian race, Black race, baseline BLyS, baseline eGFR, baseline SELENA-SELEDAI. The Likelihood ratio test, 5% significance level, was used for covariate testing. Subsequently, a covariate was considered pharmacokinetically relevant if either the R_{05} or R_{95} ratio was outside than 0.8 to 1.25 domain (the same thresholds used for bioequivalence studies) and the 95% confidence interval (CI) in the covariate parameter estimate was wholly positive or wholly negative. The R_{05} or R_{95} ratio were defined as the ratio of the model parameter at the 5th and 95th percentiles of the covariate within the study population, relative to the model parameter at the median covariate value.

The population PK analysis was performed using software NONMEM version 7.3, PsN version 4.6.0 and R version 3.2.5.

Final population PK model

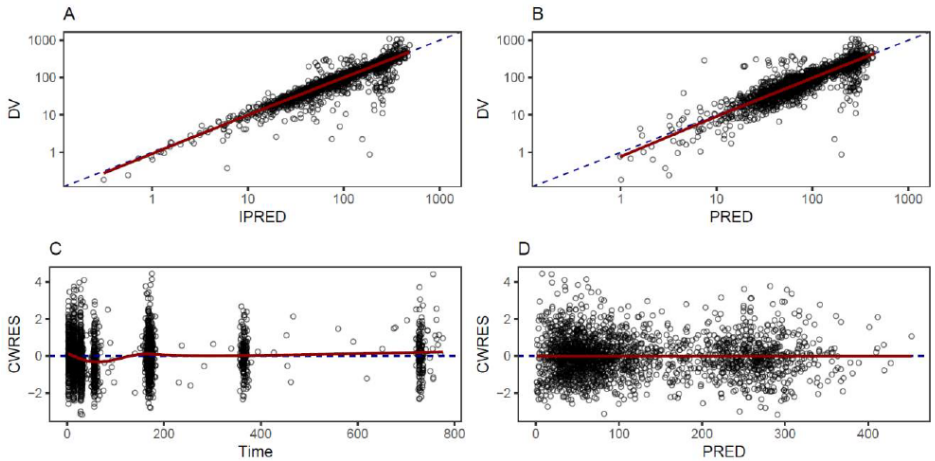
The population PK model for adults with LN was 2-compartment with first order distribution and elimination. The allometric effects of body size were best described by the fat-free mass. Albumin and proteinuria were also found to be significant time-dependent covariates of the CL. The final parameter estimates are presented in Table 3. Shrinkage in empirical Bayes estimates in CL, V1 and V2 were 4%, 17%, and 22%, respectively. Model evaluation as per goodness-of-fit plots and visual predictive checks (VPC) are presented in Table 3.

Age and Asian race were found to be statistically significant covariates of CL according to the likelihood ratio test at the 5% level of uncertainty. The CL in Asian patients with LN was predicted to be 13.7% higher than for non-Asians. However, the covariate effect for age and Asian race was not sufficiently large for the covariate to be considered pharmacokinetically relevant and so these covariates were not included in the final model.

Table 3 Fixed and Random Effect Parameters of the Final PK Model

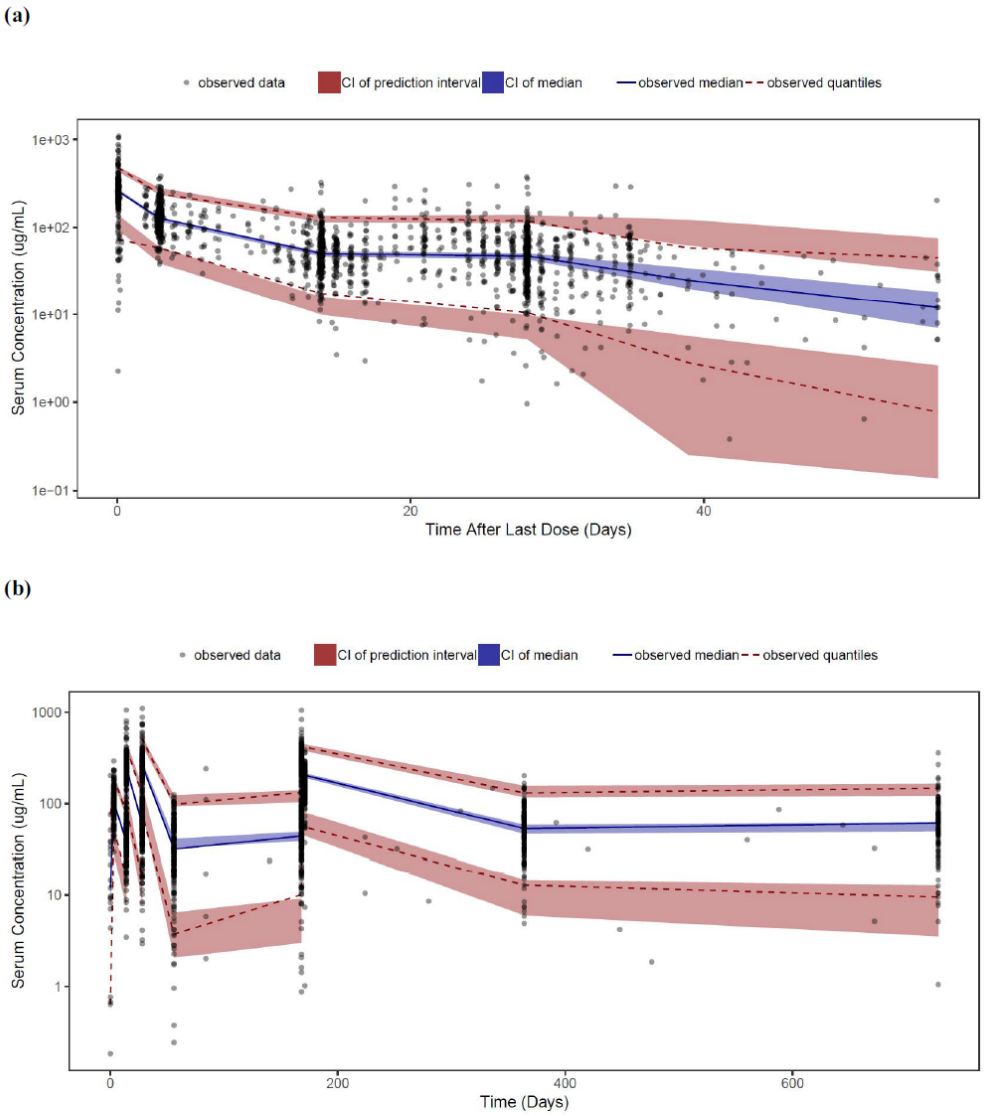
Fixed Effect Parameters		**Model Point Estimate (%RSE, 95% CI)**
CL (mL/day)		175 (2.67%, 165 - 184)
x (FFMBL / 38.4)$^{\theta}$		0.624 (16.5%, 0.422 - 0.825)
x (ALB / 42)$^{\theta 1/(1+\theta 2\times PROT)}$	θ1	-1.74 (6.13%, -1.95 to -1.53)
	θ2	0.0832 (39.5%, 0.0187 - 0.148)
x (1 + θ×PROT)		0.0663 (24.6%, 0.0344 - 0.0983)
V1 (mL)		2728 (1.82%, 2630 - 2825)
x (FFMBL / 38.4)$^{\theta}$		0.723 (13.5%, 0.531 - 0.914)
Q (mL/day)		487 (6.32%, 427 - 547)
x (FFMBL / 38.4)$^{\theta}$		See FFMBL on CL
V2 (mL)		1992 (4.99%, 1797 - 2187)
x (FFMBL / 38.4)$^{\theta}$		See FFMBL on V1
Residual variability (Normally Distributed)		**Model Point Estimate (%RSE)**
PROP		0.241 (4.47%)
ADD (μg/mL)		0.1 (Fixed)
Inter-individual variability (Log-Normally Distributed)		**Model Point Estimate (%RSE) (%CV)**
ω^2_{CL}		0.0593 (16.7%) (CV=24.7%)
ω^2_{V1}		0.0322 (33.7%) (CV=18.1%)
ω^2_{V2}		0.133 (34.3%) (CV=37.7%)
ω^2_{PROP}		0.346 (14.9%) (CV=64.3%)

Abbreviations: %RSE = relative standard error as percentage of estimate; 95% CI = the 95% confidence interval of the estimate; CL = clearance; V1 = volume of distribution for the central compartment; Q = inter-compartmental flow rate; V2 = volume of distribution for the peripheral compartment; FFMBL = fat-free mass at baseline (kg); ALB = albumin level (g/L); PROT = proteinuria level (g/g). PROP = proportional residual parameter; ADD = additive residual parameter; ω^2_{CL} = between-subject log-scale variance on CL; ω^2_{V1} = between-subject log-scale variance on V1; ω^2_{V2} = between-subject log-scale variance on V2; ω^2_{PROP} = between-subject log-scale variance on PROP and CV% = the coefficient of variation calculated as $\sqrt{(\exp(\omega^2) - 1)}$.



Abbreviations: DV = dependent variable (observed belimumab concentrations); PRED = population median predicted belimumab concentration; IPRED = individual predicted belimumab concentrations; CWRES = conditional weight residual.

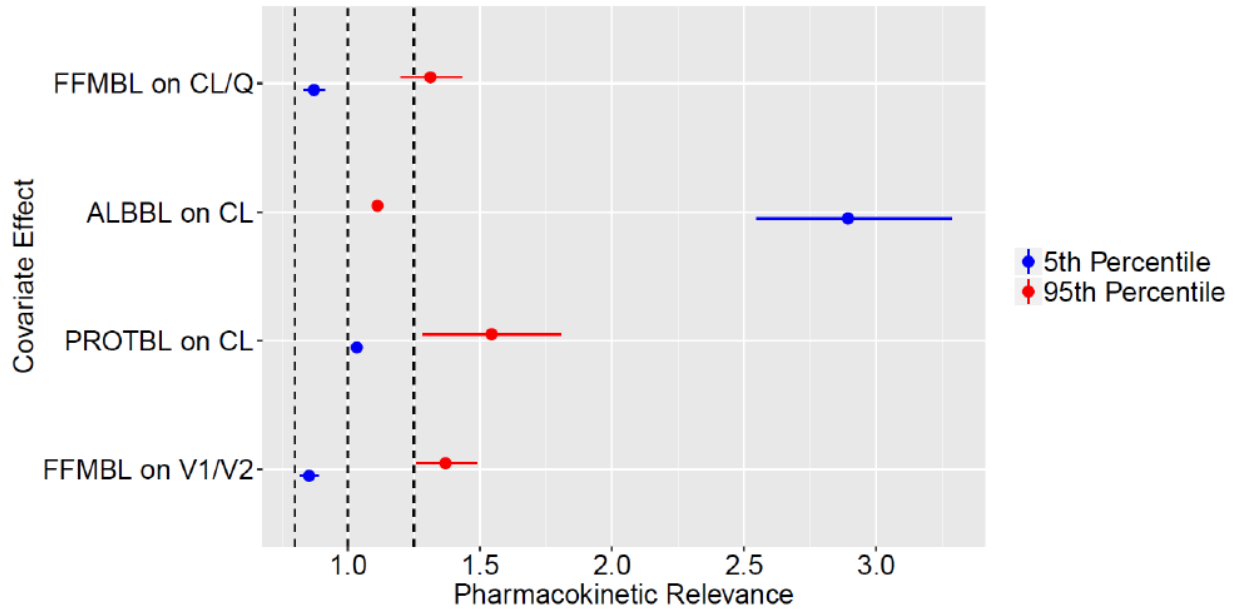
Figure 1 Goodness of fit plots comparing the observed PK of study BEL114054 with the final model predictions.



Belimumab concentration versus (a) time after last dose (b) time after first dose. Observed data (black points), observed 2.5th and 97.5th percentiles (dotted red line) with simulated 95% CI (shaded red regions); observed 50th percentile (solid blue line) with simulated 95% CI (shaded blue region).
Source: VPC.Mod102.Fig.pdf, (a) Figure 5.27 and (b) Figure 5.28.

Figure 2 VPC of observed PK from study BEL114054 for the final model.

The pharmacokinetic relevance of the covariate effects was assessed by comparing with a covariate effect of 0.8 to 1.25 on the pharmacokinetic parameter of interest (Figure 3). In the calculation of the baseline albumin effect on clearance, the proteinuria correction was partly accounted for by setting the proteinuria to its median baseline value. Thus, the effect of albumin on clearance may be over-estimated to some extent, since the true correlation between albumin and proteinuria was not fully accounted in this calculation. Additional covariates of potential clinical relevance, including sex, induction regimen (CYC or MMF), black race, baseline BLyS levels, baseline estimated glomerular filtration rate (eGFR) and baseline Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score were not found to be statistically significant covariates of belimumab CL.



The covariate effect on CL, Q, V1 and V2 at the 5th (blue point) and 95th (red point) covariate value in the study population. The 95% CI about these point estimates due to the uncertainty in the covariate parameter estimate is shown (solid lines). A covariate effect of 0.8 and 1.25 are indicated by the vertical black dotted lines. Abbreviations: FFMBL = fat-free mass at baseline; ALBBL = albumin concentration at baseline; PROTBL = proteinuria at baseline; CL = clearance; Q = inter-compartmental flow rate; V1 = central volume of distribution; V2 = peripheral volume of distribution.

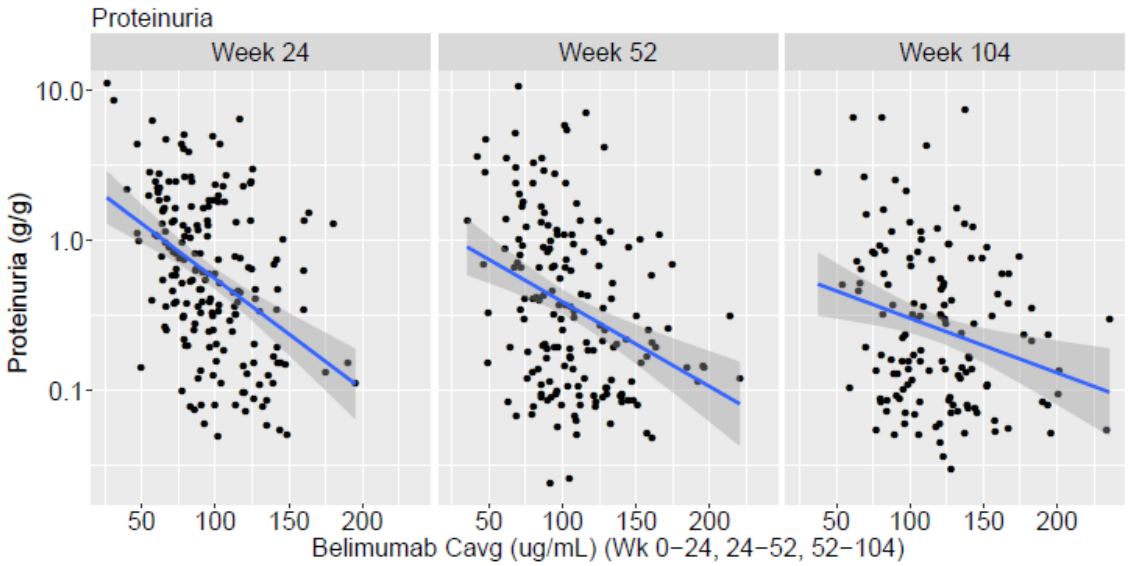
Figure 3 Covariate analysis of final model

Pharmacokinetics in Target Population

LN is a renal manifestation of SLE, with the same underlying pharmacology and mode of action for belimumab. In subjects with normal glomerular permeability, it is not expected that belimumab (molecular weight 147 kDa) would be cleared via the kidneys due to size restriction of glomerular filtration. However, in patients with LN, inflammation of the glomeruli results in an increase in elimination of intermediate molecular weight proteins and high molecular weight proteins including mAbs and immunoglobulin G (IgG). This increased urinary excretion of proteins (proteinuria) is expected to correlate with increased renal elimination of belimumab resulting in decreased systemic exposure to belimumab. This was noted in the population PK analysis for IV SLE where a higher degree of proteinuria (≥2 g/g) resulted in a 14% increase in central clearance of belimumab.

An important point to consider in the interpretation of the population PK results from BEL114054 is that all subjects started induction therapy with standard medications within 60 days of the first belimumab dose. The induction regimens result in proteinuria reduction within the first 3 to 4 months of treatment. During the first 8 to 12 weeks in both the belimumab and placebo groups, there was a rapid decline in urinary proteinuria, as measured by urine protein to creatinine ratio (Figure 4).

There is an inverse correlation between proteinuria and belimumab Cavg with high proteinuria associated with low belimumab exposure. The correlation is apparent across the duration of the study but is strongest over the first 24 weeks where the highest levels of proteinuria were observed (Figure 4).



Proteinuria levels at week 24 (left panel), at week 52 (central panel) and week 104 (right panel). Cavg is calculated from weeks 0 to 24 (left panel), weeks 24 to 52 (central panel) and weeks 52 to 104 (right panel). Individual data points (black points) with linear regression line (solid blue line). Under the null hypothesis of a zero gradient, p-values are <0.001 (left panel), <0.001 (centre panel) and 0.003 (right panel).
Source: GSK Document Number 2020N433185_00, in-text Figure 7.

Figure 4 Proteinuria Levels versus Belimumab Cavg by Time Period

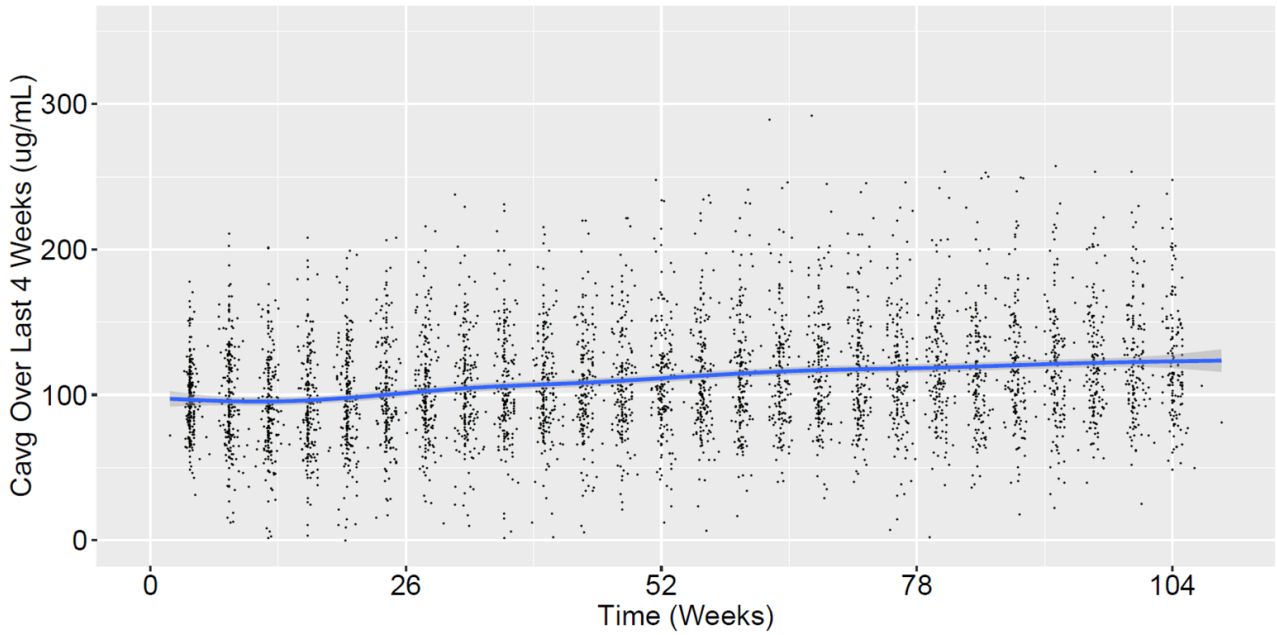
The population PK summary was derived from the final model parameters with the covariates set to their reference or default value: a 60 kg subject with 38.4 kg fat-free mass, who had no proteinuria and a normal albumin level of 42 g/L, and who received 10 mg/kg belimumab infused over 1 hour. In this scenario, the belimumab clearance and volume of distribution estimates were 175 mL/day and 4720 mL, with corresponding distributional and terminal-phase half-lives of 1.53 days and 20.0 days. The area under the curve at steady state over a 28-day dosing period was 3436 µg.day/mL, which corresponds to an average concentration of 123 µg/mL. The minimum and maximum concentrations at steady state were 67.7 µg/mL and 286 µg/mL.

At the start of treatment, estimated belimumab CL was higher in adults with LN (Table 4) compared to adults with SLE which is most likely due to the higher renal component in the CL of belimumab at the initiation of treatment. Belimumab CL decreased during the first 24 weeks of the study, and from Week 24 onwards CL was similar to that observed in the adult SLE population. This is consistent with the improvement in renal activity as shown by the decrease in proteinuria due to induction therapy.

Table 4 Estimated Steady State Clearance of Belimumab in LN Subjects

	Number of subjects	Estimated Geometric Mean Clearance (mL/day) (95% Prediction Interval)	CV(%)
Adult LN subjects			
Day 1	224	334 (174, 736)	40
Week 2	219	323 (156, 649)	40
Week 4	214	298 (143, 624)	40
Week 8	204	274 (138, 537)	39
Week 12	199	254 (138, 540)	38
Week 24	188	221 (117, 473)	37
Week 52	176	200 (112, 393)	35
Week 104	140	187 (103, 355)	34
Adult SLE subjects (GSK SLE studies)			
Belimumab at steady state	-	232 (69, 623)	34

The population PK model captured the time-dependent change on belimumab CL associated with reduction in proteinuria throughout the study. Belimumab CL was higher at Weeks 2, 4, 8 and 12 compared to Week 24, by approximately 46%, 35%, 24% and 15%, respectively (Table 4). The higher CL early in the study did not translate into a similar percent reduction in belimumab concentrations due to the administration of a loading dose at Week 2 (Figure 5). Compared to Week 24, observed pre-dose concentrations were 14% lower at Week 2, 23% higher at Week 4 and 32% lower at Week 8 (Table 5).



Individual post-hoc estimates (black points) with smooth line of best fit (blue line).

Figure 5 Individual Estimated Concentrations versus Time

Table 5 Observed Pre-Dose Belimumab Concentrations by Visit in LN Subjects

Visit	Number of Subjects (N=224)	Geometric Mean Pre-Dose Concentration (μg/mL) (95% CI)	CV%
Week 2	215	38.3 (35.6, 41.2)	59
Week 4	209	54.9 (50.3, 60.0)	73
Week 8	198	30.2 (26.7, 34.2)	107
Week 24	182	44.6 (39.5, 50.3)	100
Week 52	170	48.3 (43.6, 53.4)	75

Note: Excluded post-"Week 0" concentrations with a value of 'NQ.' (non-quantifiable).

DDI with Cyclophosphamide

The population PK analysis for BEL114054 showed that the induction regimen (CYC or MMF) was not a statistically significant covariate of belimumab clearance. Since MMF was previously shown not to have a significant impact on belimumab PK, it can be assumed that CYC would also not have a significant effect on the PK. This is supported by the similarity in the geometric mean belimumab observed pre-dose concentration in the CYC and MMF treated groups (Table 6).

Table 6 Observed Pre-Dose Belimumab Concentrations (μg/mL) by Visit (Double-Blind Phase) (Geometric Mean (CV%)

Visit	CYC BEL 10 mg/kg N=60	MMF BEL 10 mg/kg N=164	Total BEL 10 mg/kg N=224
Week 24, n	48 44.47 (126.60)	134 44.60 (90.64)	182 44.56 (99.59)
Week 52, n	42 57.19 (67.50)	128 45.64 (76.28)	170 48.26 (74.89)

Source: CSR BEL114054, Table 5.01.
Note: Excluded post-"Week 0" concentrations with a value of 'NQ.' (non-quantifiable)

2.3.3. Pharmacodynamics

According to the MAH, the pharmacodynamic responses to belimumab in subjects with LN were consistent with the known mechanism of action of belimumab and previous experience in patients with SLE [Stohl, 2012[22]] with the exception of IgG and IgG-based autoantibodies due to urinary excretion of proteins (proteinuria). In contrast to belimumab-treated SLE patients (who experienced significant reductions in IgG), in LN patients, serum IgG levels increased as a result of a rapid decline in urinary excretion of proteins over the first 8 to 12 weeks (which was to a similar extent for belimumab and placebo). Consistent with the known pharmacodynamic response of belimumab, smaller increases in serum IgG levels were observed in the belimumab group relative to placebo. At Week 104, the median percent increase from baseline in IgG was 17% for the belimumab and 37% for the placebo group.

A sensitivity analyses to control for changes in urinary IgG loss were performed for anti-double stranded DNA (anti-ds DNA) -and C1q antibodies. The results of these analyses demonstrated a notable reduction in anti-dsDNA and anti-C1q antibodies levels relative to the overall level of IgG antibodies in serum for

[22] Stohl W, Hiepe F, Latinis KM, Thomas M, Scheinberg MA, Clark A. et al. Belimumab reduces autoantibodies, normalizes low complement levels, and reduces select B cell populations in patients with systemic lupus erythematosus. Arthritis Rheum. 2012;64(7):2328-37.

subjects treated with belimumab. Subjects randomized to placebo only showed a modest reduction in the levels of autoantibodies relative to the overall level of IgG antibodies.

Increases in complement C3 and C4 in response to belimumab in LN patients are consistent with observations made in belimumab-treated SLE patients [Stohl, 2012[22]].

B cell responses to belimumab in LN patients were consistent with the mechanism of action of belimumab. Naïve B cells and memory B cells responded similarly between LN and SLE subjects treated with belimumab [Stohl, 2012[22]].

As for rare B cells subsets, these results should be interpreted with caution due to the large between-subject variability of B cell measurements,

Baseline imbalances in absolute values for total CD19+ B cells and B cell subsets were observed in subjects stratified to the different induction/maintenance subgroups but also those randomized within a subgroup; particularly noticeable in CYC/AZA-subgroup. Such baseline imbalances could affect interpretation of the degree of pharmacodynamic effects achieved by each treatment. The relatively lower total CD19+ B cells and subsets thereof observed in CYC-subgroup compared to the MMF-subgroup is likely due to the different mode of action of the induction therapies. It is been reported that CYC mainly reduces naïve and memory B cells, whilst sparing transitional B cells and late-stage B cells such as plasmablasts and plasmacells. In contrast, MMF primarily reduces late-stage B cells whilst sparing early stage B cells such as naïve and transitional B cells [Dörner, 2009[23]; Eickenberg, 2012[24]; Fassbinder, 2015[25]].

Despite the different modes of action of the drugs used in the induction and maintenance regimen, overall pharmacodynamic responses to belimumab in LN patients in the CYC-subgroup and the MMF-subgroup were consistent with the mechanism of action of belimumab.

2.3.4. PK/PD modelling

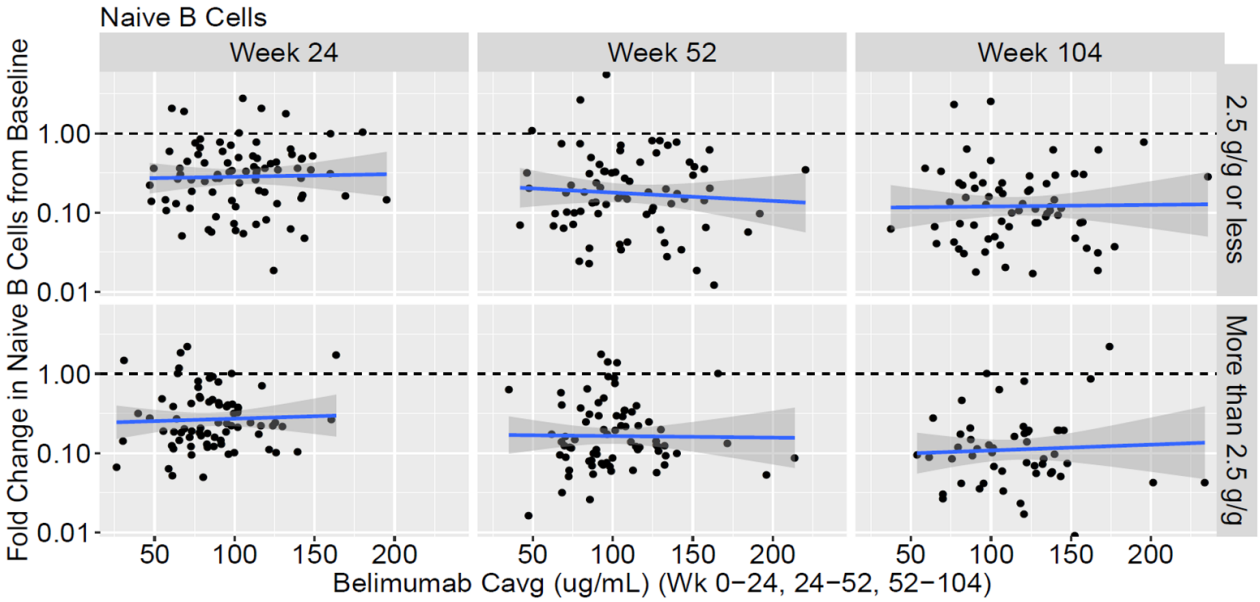
The objective of the exposure-response (E-R) analysis for BEL114054 was to evaluate whether the lower exposure to belimumab early in the study impacted the clinical response at Week 104 and whether these data suggest that a dose adjustment is required in patients with high level proteinuria.

E-R assessment for BEL114054 was limited by 2 factors. Firstly, the study was conducted at a single dose level. Secondly the E-R analysis is confounded by an association between belimumab exposure and proteinuria and between proteinuria and the efficacy endpoints primary efficacy renal response (PERR) and complete renal response (CRR) which both have proteinuria levels as a component in the definition of a responder. For PERR, a responder must achieve a urine protein to creatine ration (uPCR) ≤0.7 g/g and for CRR, a responder must achieve a uPCR <0.5 g/g.

Pharmacology Exposure Response

There is a flat relationship between naïve B-cell response and belimumab Cavg at Weeks 24, 52 and 104 in both the ≤2.5 g/g and >2.5 g/g subgroups (Figure 6). This indicates that the reduction in circulating naïve B-cell is saturated over the observed belimumab Cavg concentration range in both the low and high proteinuria subgroup during the first 24 weeks of treatment.

[23] Dörner T, Jacobi AM, Lipsky PE. B cells in autoimmunity. Arthritis Res Ther. 2009;11(5):247. (available in m5, Section 5.4)
[24] Eickenberg S, Mickholz E, Jung E, Nofer JR, Pavenstadt HJ, Jacobi AM. Mycophenolic acid counteracts B cell proliferation and plasmablast formation in patients with systemic lupus erythematosus. *Arthritis Res Ther*. 2012;14(3):R110.
[25] Fassbinder, T., Saunders, U., Mickholz, E. et al. Differential effects of cyclophosphamide and mycophenolate mofetil on cellular and serological parameters in patients with systemic lupus erythematosus. *Arthritis Res Ther*. 17, 92 (2015).



Cavg is calculated from Weeks 0 to 24 (left panel), Weeks 24 to 52 (central panel) and Weeks 52 to 104 (right panel). Individual data points (black points) with linear regression line (solid blue line) and baseline level (black dotted line). Under the null hypothesis of a zero gradient, P-values are (left to right): 0.817, 0.519, 0.901 (top row) and 0.705, 0.905, 0.692 (bottom row).

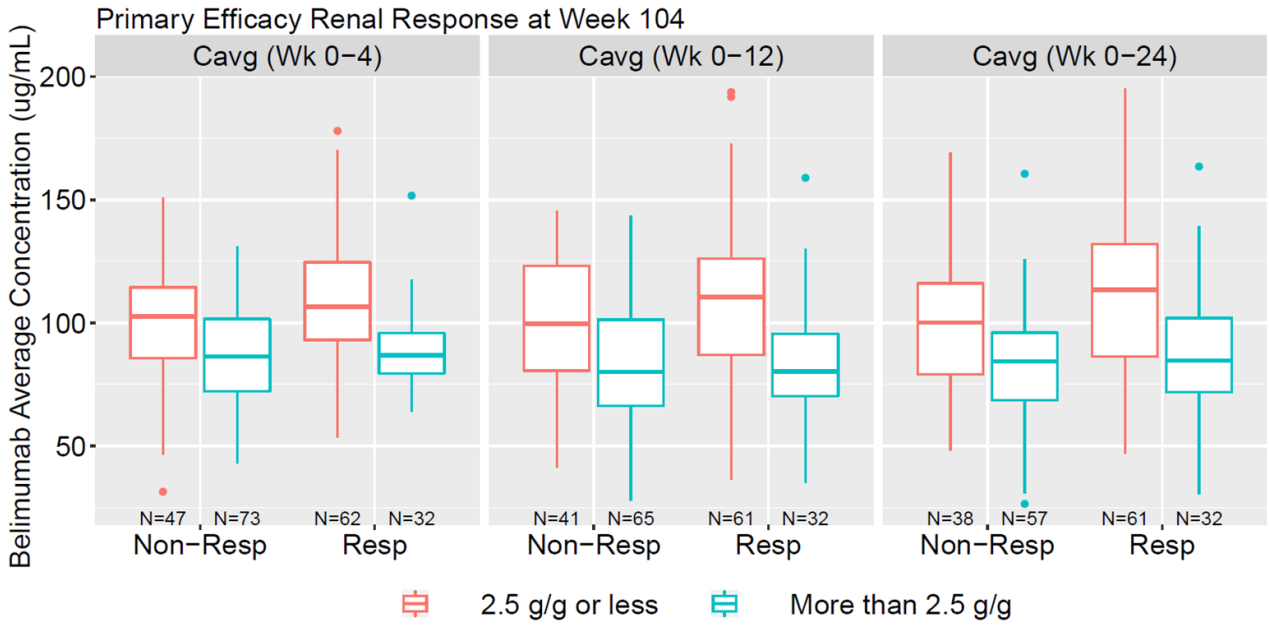
Figure 6 Naïve B Cell Response versus Average Concentration

Efficacy exposure-response

Figure 7 and Figure 8 illustrate the Cavg in non-responder and responders for PERR and CRR, respectively.

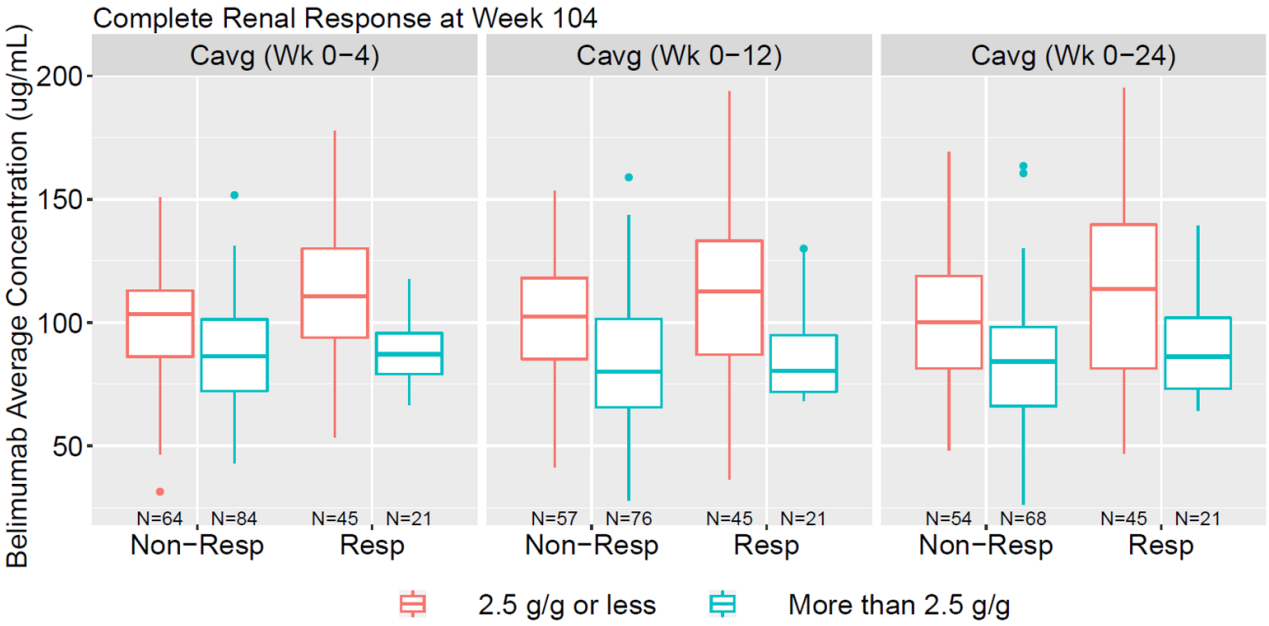
For the >2.5 g/g proteinuria subgroup median Cavg is lower than the ≤2.5 g/g subgroup. This is likely to be consequence of the higher overall renal disease activity in the >2.5 g/g baseline proteinuria subgroup which results in higher belimumab renal clearance and hence lower belimumab Cavg.

Within the >2.5 g/g baseline proteinuria subgroup, the distribution of Cavg values is similar for the non-responders and responders for both Week 104 PERR and CRR. In the ≤2.5 g/g subgroup, Cavg values appear to be slightly higher in the responders than non-responders for PERR and CRR at Week 104, but the differences were not considered meaningful. Overall, this indicates no association between response at Week 104 and belimumab Cavg values in the early weeks of the study.



Cavg is calculated from weeks 0 to 4 (left panel), weeks 0 to 12 (central panel) and weeks 0 to 24 (right panel). Box plots show the median (solid line), IQR (box), the nearest data point no more than 1.5 times above and below the box (whisker), and outlier data points (points).
Note: Efficacy response was Week 104 PERR. Subjects who discontinued IP or withdrew from study after the Cavg time period were assigned as Week 104 PERR non-responders.

Figure 7 Belimumab Cavg in PERR Non-Responders and Responders at Week 104 Stratified by Baseline Proteinuria



Cavg is calculated from weeks 0 to 4 (left panel), weeks 0 to 12 (central panel) and weeks 0 to 24 (right panel). Box plots show the median (solid line), IQR (box), the nearest data point no more than 1.5 times above and below the box (whisker), and outlier data points (points).
Note: Efficacy response was Week 104 CRR. Subjects who discontinued IP or withdrew from study after the Cavg time period were assigned as Week 104 CRR non-responders.

Figure 8 Belimumab Cavg in CRR Non-Responders and Responders at Week 104 Stratified by Baseline Proteinuria

To further elucidate if the lower percentage of PERR and CRR responders in the >2.5 g/g proteinuria subgroup was due to low belimumab exposure at the start of treatment, an assessment of belimumab Cavg Wk(0-12) by tertiles and corresponding percentage of responders was evaluated. Cavg Wk(0-12) was selected as the belimumab exposure endpoint as this represented the time period with lowest exposure to belimumab due to high proteinuria and switching from q2w to the q4w dosing regimen after Week 4.

In order to investigate if the lower percentage of responders in the >2.5 g/g baseline proteinuria subgroup was due to low belimumab exposure at the start of treatment, Cavg Wk(0-12) values were divided into tertiles and the percentage of responders within each tertile was determined for both PERR and CRR at Week 104, Table 7 and Table 8, respectively.

In the >2.5 g/g subgroup, there was no consistent trend in percentage of PERR or CRR responders across the tertiles, indicating no evidence that the lower response rates in this subgroup are related to lower belimumab exposure (Table 7).

For the ≤2.5 g/g baseline proteinuria PERR, there is some evidence of a higher percentage of PERR responders in the 2nd and 3rd tertiles compared to the 1st tertile, although percentage of PERR responders was similar in the 2nd and 3rd tertiles. For CRR the percentage of responders increased with increasing exposure tertiles (Table 8).

Table 7 Percentage of PERR and CRR Responders at Week 104 by Tertiles of Belimumab Cavg Wk(0-12) for Subjects with >2.5 g/g uPCR at Baseline

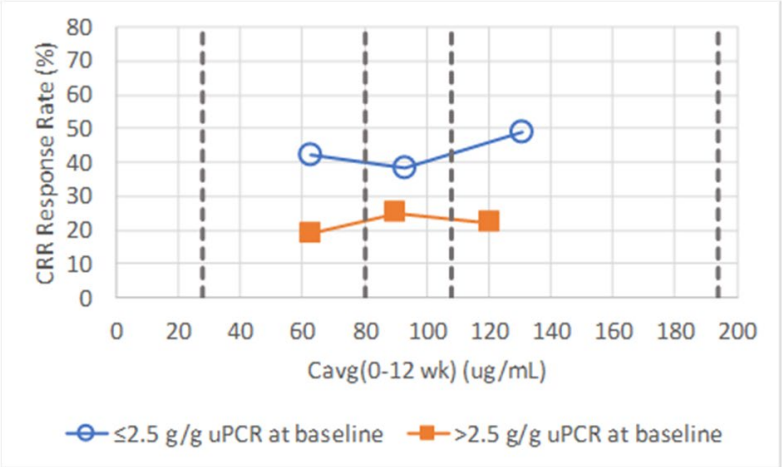
>2.5 g/g (N=97)			
	1st Tertile (N=32)	2nd Tertile (N=32)	3rd Tertile (N=33)
Belimumab Cavg Wk(0-12) Range (μg/mL)	27.9 – 72.3	72.3 – 89.2	89.2 - 159
Median Baseline Proteinuria (g/g)	5.49	3.91	3.93
PERR Responders n (%)	11 (34%)	8 (25%)	13 (39%)
CRR Responders n (%)	6 (19%)	7 (22%)	8 (24%)

Table 8 Percentage of PERR and CRR Responders at Week 104 by Tertiles of Belimumab Cavg Wk(0-12) for Subjects with Less than or Equal to 2.5 g/g uPCR at Baseline

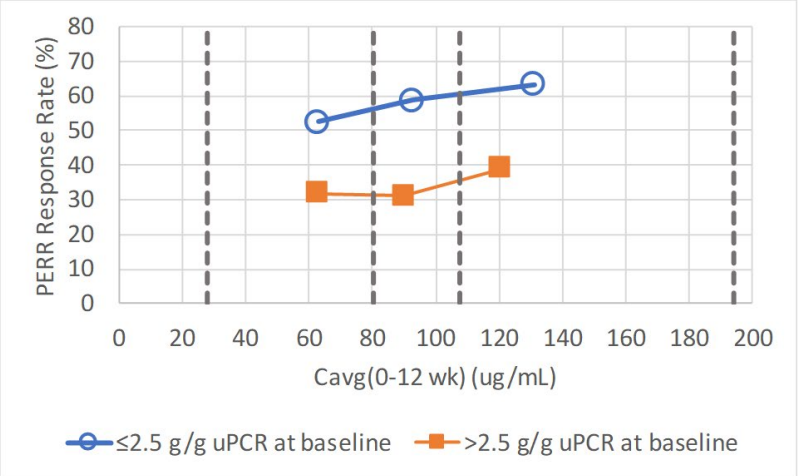
≤2.5 g/g (N=102)			
	1st Tertile (N=34)	2nd Tertile (N=34)	3rd Tertile (N=34)
Belimumab Cavg Wk(0-12) Range (μg/mL)	36.5 – 89.6	89.6– 118	119 - 194
Median Baseline Proteinuria (g/g)	1.46	1.01	0.90
PERR Responders n (%)	17 (50%)	22 (65%)	22 (65%)
CRR Responders n (%)	12 (35%)	13 (38%)	20 (59%)

For increasing tertiles of Cavg Wk(0-12), there is no consistent trend for an increase in PERR or CRR (Figure 9) response rates. For both PERR and CRR, within each belimumab Cavg Wk(0-12) tertile, the ≤2.5 g/g baseline proteinuria subgroup has approximately 20% higher response rate than the >2.5 g/g baseline proteinuria subgroup, despite having similar Cavg Wk(0-12) values.

PERR



CRR



Source: GSK Document Number 2020N433185, reproduced from in-text Table 10.

Figure 9 PERR and CRR Response Rate, split by Cavg Wk(0-12) Tertiles and then by Baseline Proteinuria

Safety exposure-response

For safety E-R, Cavg Wk(0-4) was selected as the exposure endpoint for the serious adverse events (SAEs) through Week 24 as this represented the highest exposure to belimumab early in the study due to the loading dose at Week 2. Cavg Wk(0-24) was selected as the exposure endpoint for SAEs post Week 24 as this is representative of overall systemic exposure to belimumab (Table 5).

There is no evidence of belimumab E-R relationship for the rates of reported SAEs, including serious infections (Table 9). Higher event rates of SAEs and serious infections were observed in subjects in the lowest belimumab Cavg tertile. This is likely due to a higher systemic SLE and LN activity with more significant levels of proteinuria, while receiving intensive immunosuppressive therapy and high doses of corticosteroids.

The number of patients experiencing SAEs in each exposure tertile was small, therefore the results should be interpreted with caution.

Table 9 Serious Adverse Events in Belimumab Subjects from Baseline through Week 24 by Belimumab Cavg Wk(0-4) Tertiles and Post Week 24 by Cavg Wk(20-24) Tertiles

System Organ Class[a]	Cavg Wk(0-4) Tertiles vs SAEs through Week 24		
	≤85.3 μg/mL n=72	85.3 to <106 μg/mL n=70	≥106 μg/mL n=72
Any event (n (%))	13 (18.1)	9 (12.9)	8 (11.1)
Infections and Infestations (n (%))	9 (12.5)	2 (2.9)	6 (8.3)
	Cavg Wk(20-24) Tertiles vs SAEs post Week 24		
	≤84.7 μg/mL n=62	84.7 to <115 μg/mL n=62	≥115 μg/mL n=62
Any event (n (%))	10 (16.1)	7 (11.3)	9 (14.5)
Infections and Infestations (n (%))	4 (6.5)	2 (3.2)	6 (9.7)

Source: m5.3.5.1, SAF Table 303.04 and Table 303.05.
a. Number of subjects/subgroup n (%) shown; subjects are counted only once per SOC.

Simulations to inform dose selection

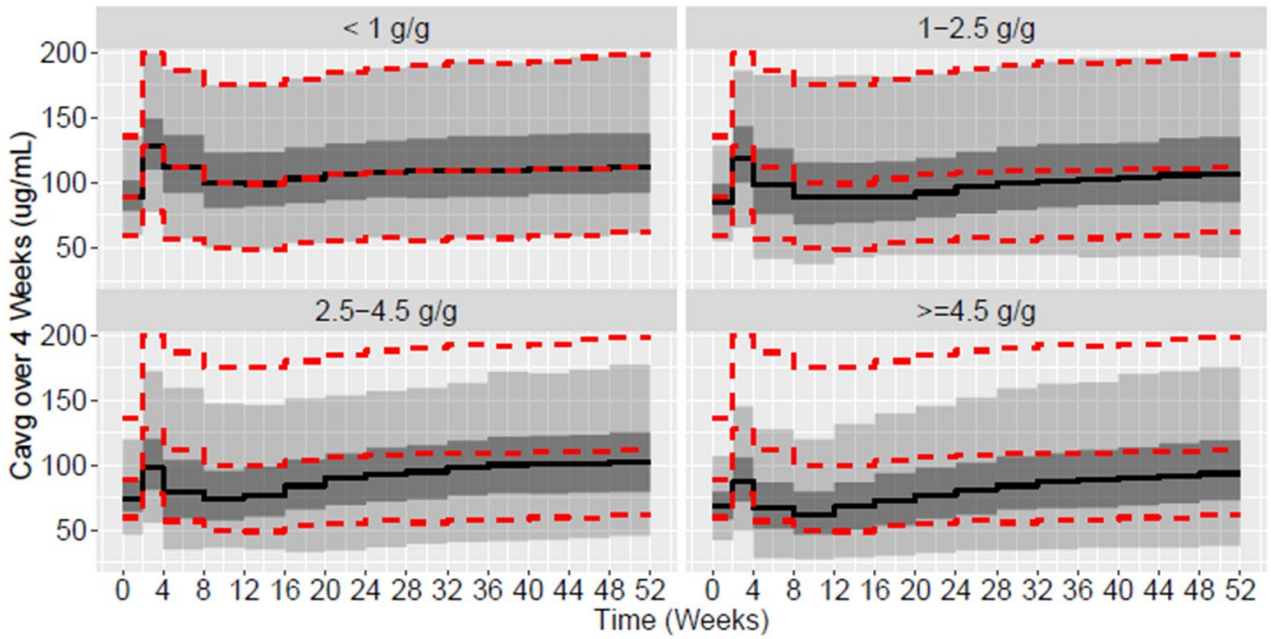
Simulations of belimumab concentration-time profiles for IV and SC dosing regimens were conducted using the population PK model fitted to the BEL114054 LN dataset. For each scenario 1000 virtual patients were simulated. The model covariates (proteinuria, albumin and baseline fat-free mass) were sampled from the BEL114054 dataset by individual with replacement, which preserved the correlation between the covariates. The entire time-course profiles for proteinuria and albumin for a sampled patient was used as the input to the PK model. Figures of simulated belimumab concentration-time profiles were summarized by the median, inter-quartile range (IQR) and 95% prediction intervals (PI). The simulations were summarized by the belimumab Cavg over 2 week time periods for the first 4 weeks and 4 week time periods, thereafter.

IV Simulations by Proteinuria Subgroup

PK simulations were conducted firstly to identify what levels of baseline proteinuria may warrant a dose adjustment based on belimumab Cavg and secondly to evaluate a dosing regimen that would provide belimumab Cavg values closest to the exposure observed in subjects with low proteinuria.

In order to identify what levels of proteinuria may benefit from dose adjustment to match PK, the belimumab treated population in BEL114054 was divided into subgroups of approximate quartiles of the baseline proteinuria (uPCR) levels: <1 g/g, 1 to 2.5 g/g, 2.5 to 4.5 g/g and >4.5 g/g.

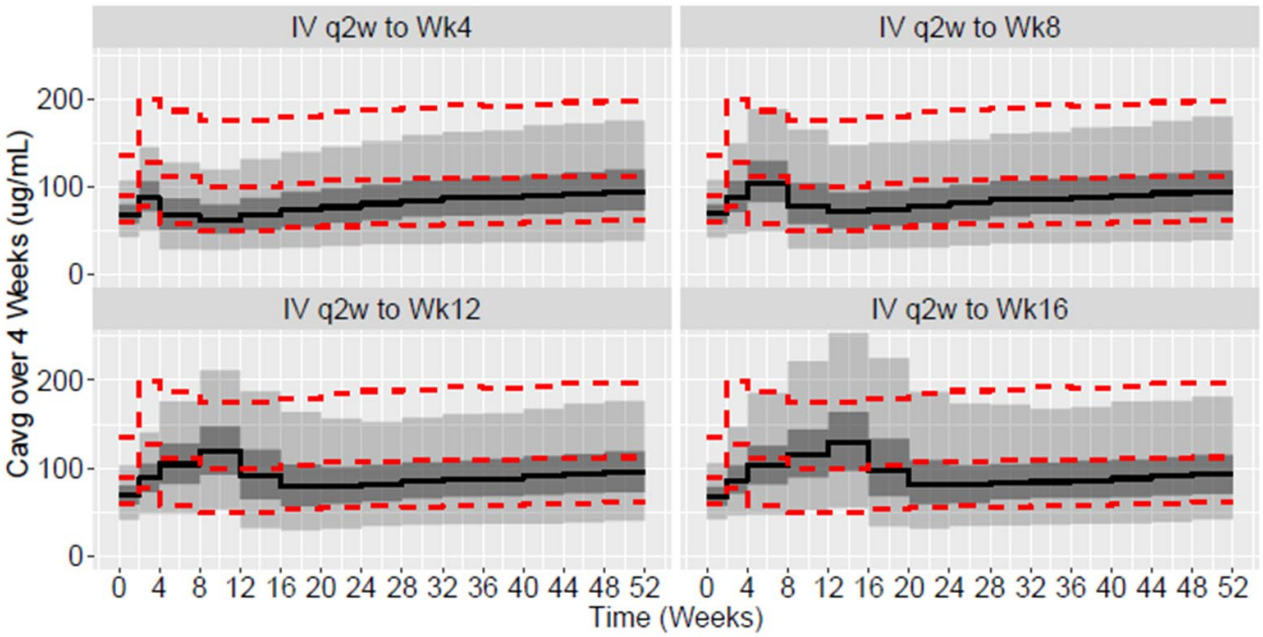
Predicted belimumab concentration time profiles for the IV dosing regimen used in BEL114054 of 10 mg/kg q2w to week 4 and q4w thereafter, were simulated for each baseline proteinuria subgroup. The <1 g/g subgroup, which is representative of the SLE patient population, was treated as the reference group. For the <1 g/g subgroup, the median Cavg over the first 12 weeks (107 μg/mL) and the first 24 weeks (105 μg/mL) of treatment were similar to belimumab Cavg,ss values in subjects with SLE (population median = 110 μg/mL and geometric mean =100 μg/mL). For the baseline proteinuria subgroups above 1 g/g, Cavg tended to be lowest during weeks 4-8, 8-12 and 12-16, compared to weeks 0-4 and weeks 16 onwards (Figure 10). The belimumab Cavg for the 1 to 2.5 g/g and 2.5 to 4.5 g/g was within 30% of the <1 g/g subgroup. For the >4.5 g/g subgroup, the Cavg was within 40% of the <1 g/g subgroup.



Solid line black line represents median belimumab concentration. Dark grey shaded area represents interquartile range, Light grey shaded area represents 95% prediction interval. Red dashed lines represent median and 95% prediction interval of reference <1 g/g uPCR baseline.

Figure 10 Simulations of Belimumab Cavg over 4-week Time Periods Following Administration of IV 10 mg/kg q2w to Week 4 and q4w thereafter for Baseline Proteinuria Subgroups

For the >4.5 g/g baseline proteinuria subgroup, alternative IV q2w loading dose durations were evaluated and compared to Cavg for <1 g/g subgroup with the standard q2w to week 4 regimen. Durations of loading doses to weeks 8, 12 and 16 were simulated each followed by q4w thereafter (Figure 11).



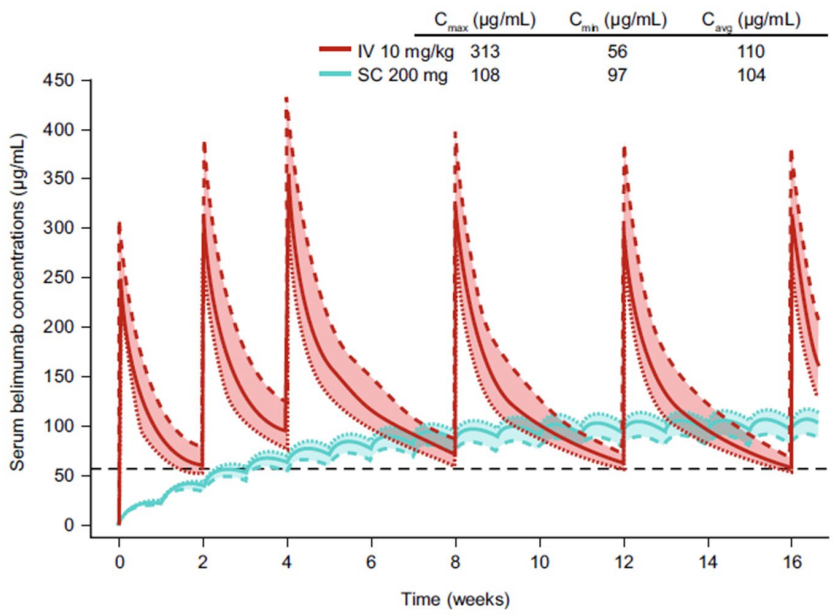
Solid line black line represents median belimumab concentration. Dark grey shaded area represents interquartile range, Light grey shaded area represents 95% prediction interval. Red dashed lines represent median and 95% prediction interval of reference <1 g/g uPCR baseline.

Figure 11 Simulations of Belimumab Cavg over 4 Week Time Periods (>4.5 g/g Baseline Proteinuria Subgroup) Following Administration of IV 10 mg/kg q2w for 4, 8, 12 and 16 Weeks followed by q4w Dosing

The simulations showed that in subjects with baseline proteinuria values >4.5 g/g IV dosing of 10 mg/kg q2w up to week 12 with 10 mg/kg q4w thereafter, provided the closest match to the predicted belimumab Cavg values in the <1 g/g subgroup following IV 10 mg/kg q2w up to week 2 with 10 mg/kg q4w thereafter.

SC Simulations by Proteinuria Subgroup

The results from the pivotal SC Phase III efficacy study in adults with SLE (BEL112341) showed that 200 mg q1w results in a similar pharmacological and efficacy response as the IV dose regimen of 10 mg/kg q4w. Population PK modelling and simulations showed that for SC 200 mg q1w the belimumab Cavg,ss of 100 μg/mL was similar to the IV 10 mg/kg q4w Cavg,ss of 110 μg/mL (Figure 12).



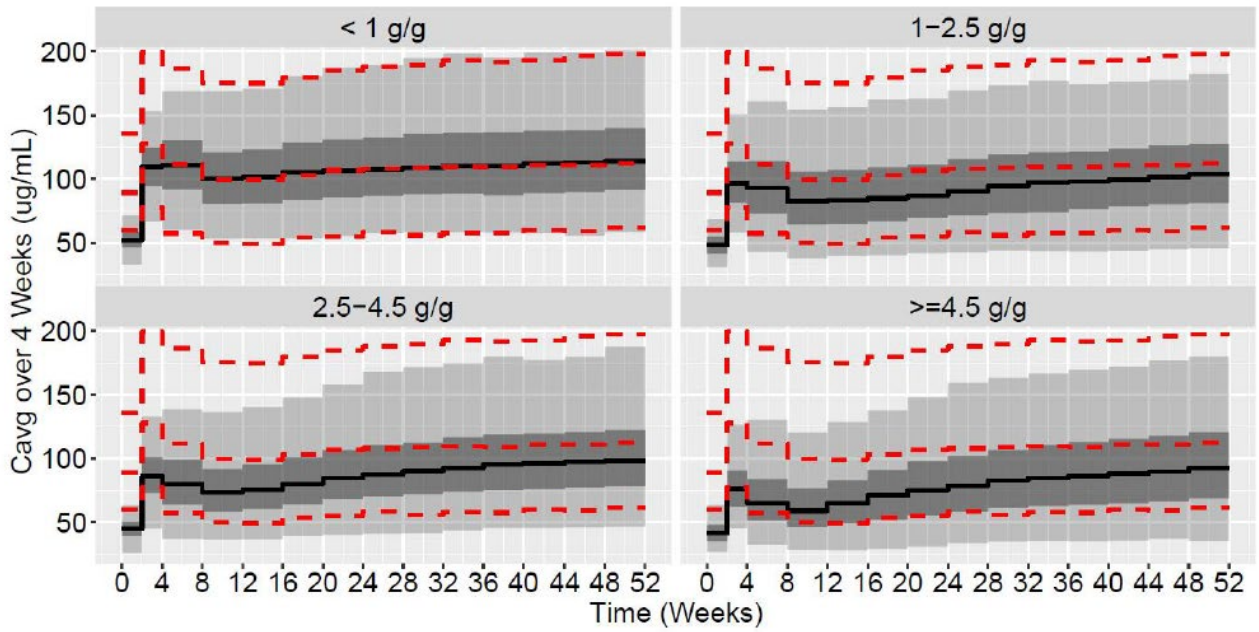
Source: [Struemper, 2018].

Figure 12 Simulations of PK profile and SS PK parameters for Belimumab IV 10 mg/kg q2w to Week 4, then IV 10 mg/kg q4w vs SC 200mg q1w in Subjects with SLE

The population PK model developed for the adult LN population was extended to include SC dosing by incorporating the absorption component of the population PK model developed from the adult SLE analysis (lag time of 0.179 days and absorption rate constant of 0.235 h-1 which corresponds to a half-life of 2.9 days) [Struemper, 2018[26]]. It was assumed that bioavailability for SC administration of belimumab in LN population was similar to that observed in SLE (74.2%).

Simulations were conducted to evaluate the predicted impact of proteinuria on Cavg following SC administration and alternative SC regimens to achieve similar Cavg in subjects with <1 g/g. In doing so, the weekly regimen was maintained but the SC dose was doubled i.e., for <4.5 g/g loading doses of 400 mg q1w up to Week 4 followed by 200 mg q1w thereafter and for >4.5 g/g baseline proteinuria subgroup, loading doses of 400 mg q1w up to Week 12 followed by 200 mg q1w thereafter. These simulations showed that SC 400 mg loading doses provided belimumab Cavg values were comparable to the corresponding IV loading doses to Week 4 in all proteinuria subgroups (Figure 13 and Table 10) and to Week 12 for the ≥4.5 g/g baseline proteinuria subgroup (Table 11).

[26] Struemper H, Chen C, Cai, W. Population pharmacokinetics of belimumab following intravenous administration in patients with systemic lupus erythematosus. *J Clin Pharmacol*. 2013;53:711-20



The median values (solid black line) is shown with the inter-quartile range (dark grey area) and 95% prediction interval (light grey area). The dotted red lines represent the median and 95% prediction interval for the reference population: patients with baseline proteinuria less than 1 g/g who received IV belimumab with IV loading to week 4, the SLE approved dose. Source Figure 12.

Figure 13 Average exposure versus time: SC dosing with loading to week 4.

Table 10 Predicted Belimumab Cavg values Following IV 10 mg/kg q2w to Week 4 Followed by 10 mg /kg q4w thereafter and SC Doses of 400 mg q1w to Week 4 Followed by 200 mg q1w

	<1 g/g		1 to 2.5 g/g		2.5 to 4.5 g/g		≥4.5 g/g	
	IV	SC	IV	SC	IV	SC	IV	SC
Weeks	Cavg (μg/mL)							
0-2	89	52	85	48	74	45	68	41
2-4	128	110	119	97	98	86	87	76
4-8	112	111	99	93	80	80	67	65
8-12	100	100	89	82	75	73	62	59
12-16	99	101	89	83	77	76	68	65
16-20	103	105	89	85	84	80	73	71
20-24	107	106	93	87	90	85	77	75
24-28	108	108	97	90	93	88	81	79
28-32	109	109	100	94	95	90	84	83
0-12	**107**	**97**	**98**	**83**	**80**	**73**	**69**	**61**

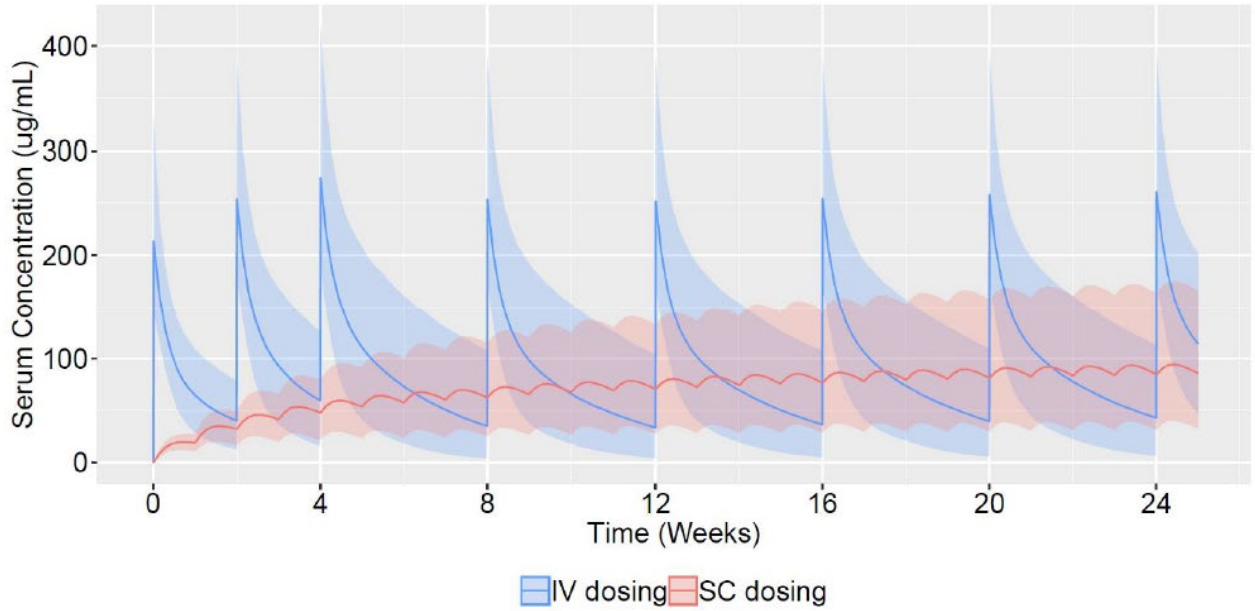
Table 11 Predicted Belimumab Cavg following IV 10 mg/kg q2w to Week 12 Followed by 10 mg/kg q4w thereafter and SC Loading Doses of 400 mg q1w to Week 12 Followed by 200 mg q1w thereafter (>4.5 g/g Baseline Proteinuria Subgroup)

Weeks	≥4.5 g/g	
	IV Cavg (μg/mL)	SC Cavg (μg/mL)
0-2	69	42
2-4	89	78
4-8	104	100
8-12	119	116
12-16	91	96
16-20	79	79
20-24	79	77
24-28	82	80
28-32	85	84
0-12	**100**	**92**

Simulations showed that belimumab Cavg values for SC loading doses of 400 mg q1w were similar to IV loading dose of 10 mg /kg q2w and that belimumab Cavg was also similar for the subsequent standard dosing of IV 10 mg/kg q4w and SC 200 mg q1w.

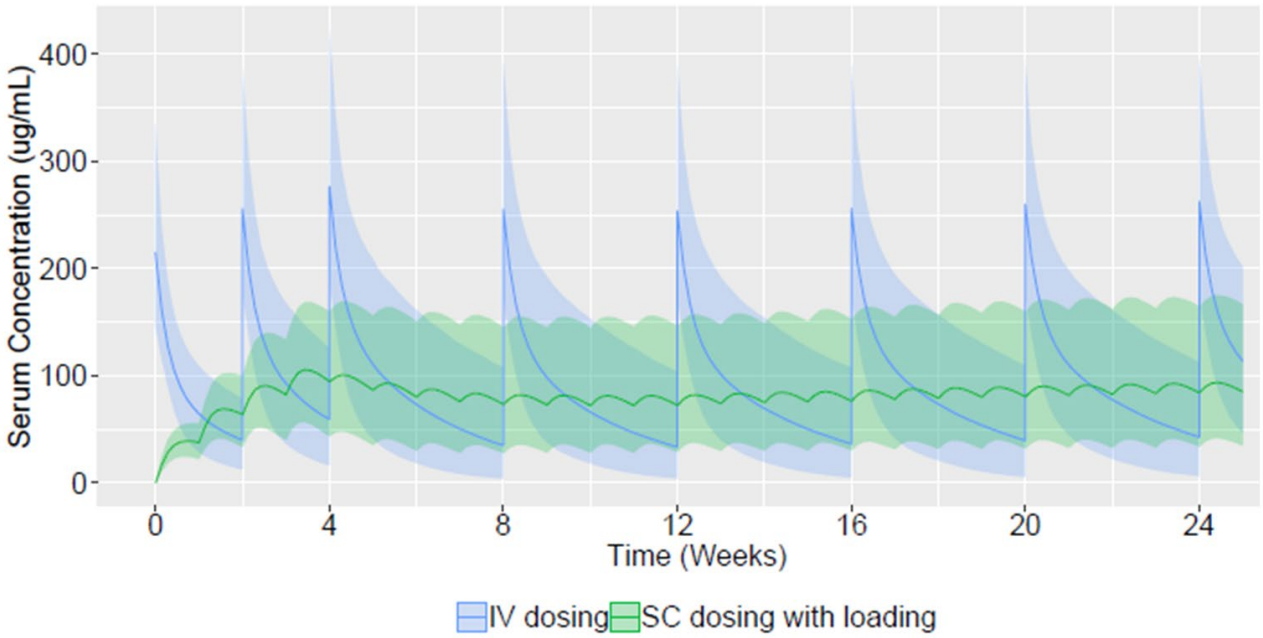
SC simulations for the full LN population

The current approved SC regimen of 200 mg q1w does not achieve belimumab steady-state concentrations until approximately week 12 and the exposure to belimumab is lower than the IV dosing regimen during the first 8 weeks of dosing (Figure 14). The phase 3 study in subjects with SLE (BEL112341) showed that the efficacy response following SC dosing is similar to that for IV, and so the absence of a SC loading regimen was not detrimental to treatment outcome. PK simulations have been used to show how introducing a SC loading regimen to all patients, irrespective of proteinuria levels, raises belimumab exposure over the first 12 to 24 weeks of treatment in line with exposures following IV dosing. These loading doses provide similar belimumab exposures to those achieved with the IV dosing regimen of 10 mg/kg q2w to week 4, followed by 10 mg/kg q4w thereafter. The predicted belimumab concentration-time profiles for all proteinuria subgroups for the proposed IV and SC dose regimens are provided in Figure 15 and predicted belimumab Cavg values for the both regimens along with the standard SC 200 mg q1w dosing are provided in Table 12.



The median values (solid line) is shown with the 95% prediction interval (shaded region) for 10 mg/kg IV (with IV loading to week 4) and SC dosing (with no loading). Source Figure 19.

Figure 14 Concentration versus time: 10 mg/kg IV with loading to week 4 and SC dosing with no loading.



Solid line represents median belimumab concentration. Shaded area represents 95% prediction interval.

Figure 15 Simulations of Belimumab Serum Concentration-Time Profiles Following Administration of SC 400mg q1w to Week 4 Followed by 200 mg q1w thereafter Superimposed on IV 10 mg/kg q2w to Week 4 and q4w thereafter (All Proteinuria Subgroups Combined)

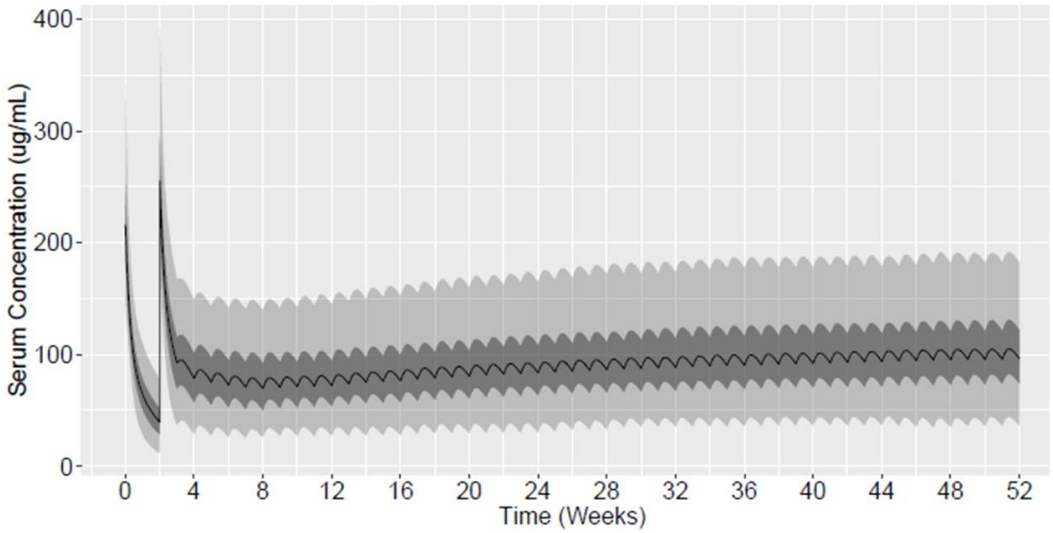
Table 12 Predicted Median Belimumab Cavg Values Following Administration of IV 10 mg/kg q2w to Week 4 Followed by 10 mg /kg q4w Thereafter and SC 400 mg q1w to Week 4 Followed by 200 mg q1w Thereafter Compared to 200 mg q1w (All Proteinuria Subgroups Combined)

Weeks	IV 10 mg/kg q2w to Wk 4 then q4w	SC 400 mg q1w to Wk 4 then 200 mg q1w	SC 200 mg q1w
	Cavg (μg/mL)		
0-2	80	47	24
2-4	109	92	47
4-8	90	87	62
8-12	81	78	73
12-16	84	81	80
16-20	88	85	85
20-24	92	88	89
24-28	95	91	92
28-32	97	94	94
0-12	**89**	**78**	**57**

The SC dosing regimen has higher predicted belimumab Cmin and lower belimumab Cmax and similar belimumab Cavg values compared to the IV dosing regimen. This suggests that SC dosing regimen should provide similar efficacy and safety to that observed with IV.

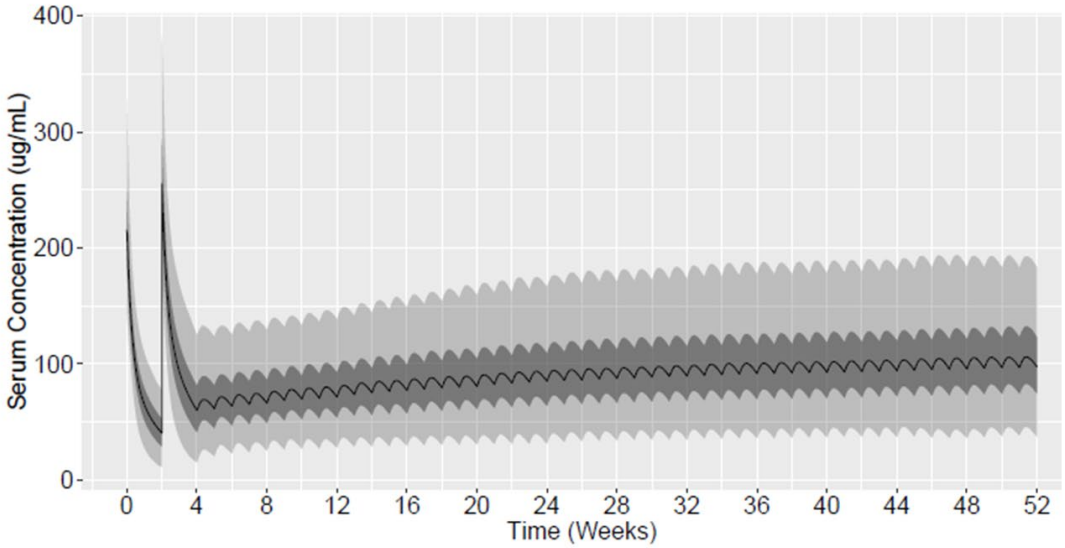
Switching from IV to SC

For the 10 mg/kg IV dose with loading to week 4 (that is, an extra IV dose administered at week 2 as for SLE), the switch to SC can be made at week 3 (Figure 16) or at week 4 (Figure 17). Providing the first two IV doses are administered on days 0 and 14, it is considered acceptable making the switch to SC 1 to 2 weeks after the last IV dose. The same recommendation will equally apply at later times as proteinuria levels are expected to be lower and exposures closer to steady state when the switch to SC dosing is made.



Solid black line represents median belimumab concentration, dark grey shaded area represents interquartile range, light grey represents 95% prediction interval.

Figure 16 Simulations of Belimumab Serum Concentration-Time Profiles Following Administration of IV 10 mg/kg Q2w for 2 Doses Followed by SC 200mg q1w 1 Week After the IV Dose At Week 2 (All Proteinuria Subgroups Combined)



Solid black line represents median belimumab concentration, dark grey shaded area represents interquartile range, light grey represents 95% prediction interval.

Figure 17 Simulations of Belimumab Serum Concentration-Time Profiles Following Administration of IV 10 mg/kg q2w for 2 Doses Followed by SC 200mg q1w 2 Weeks After the IV Dose at Week 2 (All Proteinuria Subgroups Combined)

Switching to SC 1 or 2 weeks after the 2nd IV dose resulted in belimumab Cavg values similar to those that achieved with IV 10 mg/kg q4w from week 4 onwards (Table 13). Therefore, if a patent with LN switches from IV to SC they can have the 1st SC dose between 1 and 2 weeks after the last IV dose.

Table 13 Predicted Belimumab Cavg Values Following Administration of IV 10 mg/kg q2w for 2 Doses Followed by SC 200 mg Q1w at 1 and 2 Weeks After Last IV Dose (All Proteinuria Subgroups Combined)

	IV 10 mg/kg q2w for 2 doses and then switch to:		
	IV 10 mg/kg q4w at Wk 4	SC 200 mg q1w at Wk 3	SC 200 mg q1w at Wk 4
Week	Cavg (μg/mL)		
0 - 2	80	80	80
2 - 4	109	117	109
4 - 8	90	79	69
8 - 12	81	77	75
12 - 16	84	80	81
16 - 20	88	85	85
20 - 24	92	88	89
24 - 28	95	91	92
28 - 32	97	93	94
0 - 12	**89**	**85**	**81**

2.3.5. Discussion on clinical pharmacology

In order to support dosing recommendations in LN population, the MAH performed population PK analysis from 448 randomized to placebo (n=224) or belimumab (n=224) in the double-blind phase of study BEL114054 and E-R analysis for study BEL114054.

The bioassays used in this application have been previously submitted. The same cut-point used in the bioassay for anti-belimumab antibodies in the SLE population was used in the LN population. This is considered a conservative approach since the false positive ADA rate was somewhat higher in the LN population and thus accepted by the CHMP. The pharmacokinetics of belimumab in the LN patient population was characterised by population PK modelling. A 2-compartment with first order distribution and elimination was identified, consistent with the previous PK analysis in adults with SLE. The allometric effects of body size were best described by the fat-free mass. Albumin and proteinuria were also found to be significant time-dependent covariates of the CL. Thirteen percent of the PK data collected were excluded from the PK model development, of which 12% were below limit of quantification. Although excluding BLQ data could have an impact on the estimated CL/F value, the CHMP considers that the data exclusion was not expected to impact the dose selection. Overall, the CHMP considers that the final model appropriately describes the PK data in the LN population.

At the start of randomized treatment in adults with LN in Study BEL114054, estimated belimumab CL (~334 mL/day) was higher than for adults with SLE (232 mL/day) due to renal disease. Belimumab CL decreased during the first 24 weeks of the study, and from Week 24 onwards, was similar to that observed in the adult SLE population. The average difference in CL at week 2 and week 24 was 46%. The time-varying CL is largely attributed to the reduction in proteinuria over time (decreased proteinuria leads to increased exposure). The effect of body size on belimumab PK was best described by fat-free mass. Section 5.2 of the SmPC is updated with results on population PK analysis in LN patients.

According to the population PK analysis, as well as observed belimumab concentrations, no influence of concomitant use of cyclophosphamide on belimumab PK was observed. Section 4.4 of the SmPC is

updated to remove the statement on the absence of studies on Benlysta use in combination with cyclophosphamide and to remove caution to be exercised if Benlysta is co-administered with Benlysta.

Exposure-response

There was no trend with increasing B cell response with increasing belimumab concentration, for either high or low proteinuria subgroups.

The graphical analysis on exposure versus responder/non-responder, stratified on proteinuria, suggests a minor difference in exposure between responders and non-responders. Nonetheless, there is a consistent higher response rate in the low proteinuria group. Graphical analysis did not provide evidence to suggest that an increase in belimumab systemic exposure via dosage adjustment would improve clinical efficacy response in subjects with high baseline proteinuria. However, the efficacy E-R evaluation was limited by the fact that only 1 dose level was studied, and that proteinuria was a confounding factor affecting both belimumab exposure and efficacy outcomes. Thus, E-R modelling on the data from study BEL114054 are not considered meaningful as it is not possible to discriminate between the influence of exposure and proteinuria due to the high correlation between the two factors and that proteinuria is not independent of the response variable.

The number of patients with SAEs in each exposure tertile was small and thus the results were interpreted with caution. Nonetheless, no apparent trend with increasing SAEs with increasing exposure was detected. A higher incidence of SAEs in the low exposure group, could potentially be correlated to a highly active disease (i.e. high proteinuria) in this group.

Simulations to support dose selection

Since the interpretation of the exposure-response results are limited by confounding factors (correlation between proteinuria and exposure), there is no evidence confirming that an increase in exposure (via dose adjustment to match PK in patients with low proteinuria) for LN patients with high proteinuria at baseline would improve efficacy outcome. Therefore, the CHMP agreed that the proposed IV dosing regimen for LN is the same as SLE for all proteinuria subgroups i.e., 10 mg/kg q2w to week 4 then 10 mg/kg q4w.

PK simulations for the SC dosing were provided for the LN population PK model by incorporating the absorption parameters from the SLE SC population PK model. The assumption that the SC absorption is similar between the two patient populations is endorsed by the CHMP. According to the simulation results, the best match between IV and SC exposure was achieved when a SC loading dose of 400 mg was administered q1w, week 1-4, followed by 200 mg q1w. Population PK modelling and simulation results supporting the dose selection have been appropriately included in Section 5.2 of the SmPC.

Simulations to support a recommendation for transitioning between IV and SC administration were presented. The simulations indicate that the preferred timeframe for a switch to SC dosing would be 1-2 weeks after the last IV dose to maintain steady-state concentration levels. This is endorsed by the CHMP.

2.3.6. Conclusions on clinical pharmacology

The PK of belimumab in the LN population is well described and the simulations to support dose selection are adequate. The following dosing recommendations are agreed by CHMP:

- IV dosing: 10 mg/kg q2w to week 4 then 10 mg/kg q4w.

- SC dosing: loading dose of 400 mg administered q1w, week 1-4, followed by 200 mg q1w

- transition from IV to SC administration: the first dose of 200 mg subcutaneous injection should be administered 1 to 2 weeks after the last IV dose. This transition should occur any time after the patient

completes the first 2 IV doses.

2.4. Clinical efficacy

2.4.1. Main study

Study BEL114054 ("BLISS-LN")

Methods

This was a Phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled, 104-week study to evaluate the efficacy and safety of IV belimumab 10 mg/kg plus standard of care compared to placebo plus standard of care in adult subjects with active LN (histological classes III, IV, V or V in combination with III or IV LN).

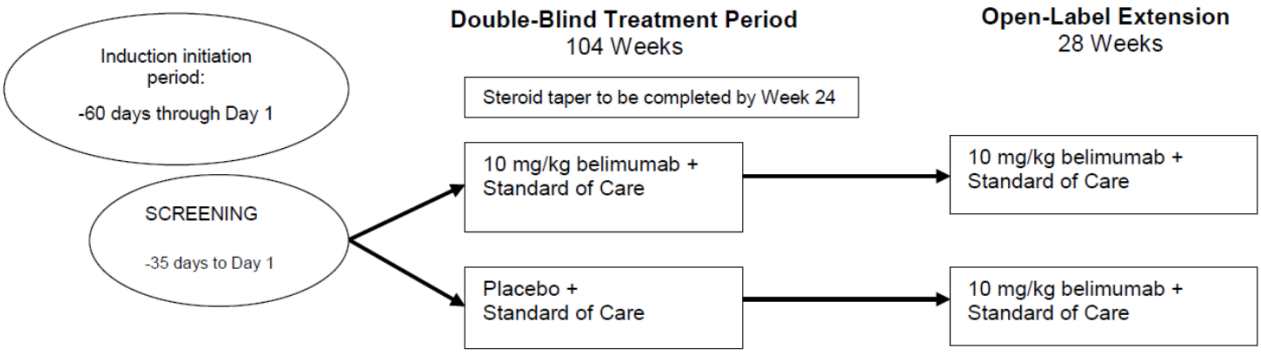


Figure 18. Overview of study design

Study participants

Subjects enrolled in the study must have met the following inclusion criteria:

1. Males or females at least 18 years of age.
2. Have a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria.
3. Have active, biopsy-proven proliferative lupus nephritis Class III or IV [excluding Class III(C), IV-S(C), and IV-G(C)] either with or without the presence of Class V, or pure Class V membranous using the 2003 ISN/RPS criteria; the biopsy must be performed in the 6 months prior to the screening visitor during the screening period.
4. Have unequivocally positive anti-nuclear antibody (ANA) test results defined as an ANA titer ≥ 1:80(based on Hep-2 immunofluorescence assay or equivalence by enzyme immunoassay assay), and/or a positive anti-dsDNA (≥ 30 IU/mL based on ELISA assay) serum antibody test at the screening visit based on the study's central laboratory results.
5. Have documentation of active renal disease at screening requiring induction therapy with high dose corticosteroids (HDCS) with either IV CYC or MMF or other oral forms of mycophenolate.

The following factors were used to define active renal disease at screening:

Urinary protein: creatinine ratio of ≥1.0 AND

- Active urinary sediment as defined by at least 1 of the following (in absence of menses and genitourinary tract infection).
    - 5 red blood cell (RBC)/high power field (hpf) or above the laboratory reference range
    - 5 white blood cell (WBC)/hpf or above the laboratory reference range.
    - Presence of cellular casts (RBC or WBC).
- Subjects without active urinary sediment were eligible if they met at least 1 of the following criteria:
    - A confirmatory biopsy performed within 3 months prior to the screening visit or during the screening period meeting the biopsy criteria outlined above.
    - Proteinuria ≥3.5 grams/day (or urinary protein:creatinine ratio≥3.5).

Key exclusion criteria included subjects who previously failed both CYC and MMF (or other forms of mycophenolate) induction therapies based on the investigator's opinion. Other key exclusion criteria included: severe active central nervous system (CNS) lupus; a history of malignant neoplasm within the last 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma *in situ* of the uterine cervix; required management of acute or chronic infections within 60 days of Day 1; receipt of specific treatments/therapy (e.g., B cell targeted therapy, any biologic agent other than B cell targeted therapy, plasmapheresis, non-biologic investigational agent, a live vaccine) within protocol-defined timeframes prior to Day 1; subjects who had been on dialysis within 364 days of baseline (Day 1), and subjects who had an estimated glomerular filtration rate <30mL/min/1.73m^2 at the screening visit.

Treatments

The double-blind treatment groups included one active treatment arm of 10 mg/kg belimumab and a placebo arm, with all treatment groups receiving standard of care therapy.

Subjects was dosed with study agent on Days 0 (baseline), 14, 28 and then every 28 days thereafter through 100 weeks with a final evaluation for the double-blind treatment period at 104 weeks. All subjects received background therapy consisting of one of the following standard of care regimens:

- High Dose Corticosteroids (HDCS) + Cyclophosphamide (CYC) for induction therapy followed by Azathioprine (AZA)for maintenance therapy

  OR

- HDCS+ Mycophenolate Mofetil (MMF) for induction therapy followed by MMF for maintenance therapy

The study recommended corticosteroid regimen included 0-3 IV pulses of methylprednisolone 500mg-1000mg/pulse followed by oral prednisone at a recommended dose of 0.5-1.0 mg/kg/day with total daily dose up to 60 mg/day. Adjustments could be made for tolerability issues. It was recommended that oral corticosteroids should be tapered according to Table 14. If necessary, it could take longer than 12 weeks to complete the taper. By Week 24, the dose of corticosteroids should be at 10 mg of prednisone/day or less (can be 0 mg) or subject was considered a treatment failure.

The randomization of all eligible subjects was stratified by their induction/maintenance regimen (HDCS plus CYC followed by AZA vs HDCS plus MMF followed by MMF) and race (black race vs other).

Table 14. Recommended oral prednisone taper regimen

Study Week	Reduced Dose (mg/day)
0	60
2	50
3	45
4	40
5	35
6	30
7	25
8	20
9	17.5
10	15
11	12.5
12	10

Immunosuppressives

Other immunosuppressives (eg, methotrexate [MTX]) were allowed provided these were started prior to baseline and met eligibility criteria. Dose alterations during the trial of these agents were permitted. Subjects who newly initiated immunosuppressives (with the exception of topical agents) after the baseline visit outside the induction regimen was considered treatment failures.

Angiotensin Pathway Antihypertensives

Starting a new angiotensin pathway antihypertensive (ACE inhibitor, angiotensin receptor blocker) treatment after the Week 24 visit would cause the subject to be declared a treatment failure. Dose titration was allowed.

Antimalarials

A subject starting antimalarial treatment after the Week 24 visit was declared a treatment failure.

Objectives

The objectives of this study were to evaluate the efficacy, safety and tolerability of belimumab with standard of care versus placebo plus standard of care in adult subjects with lupus nephritis Class III, IV, and/or V using the 2003 ISN/RPS criteria.

Outcomes/endpoints

The primary and 4 major secondary endpoints in Study BEL114054 are described in Table 15.

Table 15 Primary and Major Secondary Endpoints in BEL114054

Endpoint	Definition
Primary Endpoint	
Primary Efficacy Renal Response (PERR) at Week 104 measured as a dichotomous response (Responder vs. Non-Responder). Determined by reproducible changes in proteinuria and renal function. Analysed using logistic regression.	The PERR at Week 104 is defined by a response at the Week 100 visit that is confirmed by a repeat measurement at the Week 104 visit. **Responder**: urine protein to creatine ration (uPCR) ≤0.7 and eGFR is no more than 20% below pre-flare value or ≥60 mL/min/1.73m^2 and-Not a Treatment Failure[a] **Non-Responder:** Not meeting criteria for PERR renal response
Major Secondary Endpoints	
Complete renal response (CRR) at Week 104 Determined by reproducible changes in proteinuria and renal function defined by a response at the Week 100 visit that is confirmed by a repeat measurement at the Week 104 visit. Analysed using logistic regression.	The CRR at Week 104 is defined by a response at the Week 100 visit that is confirmed by a repeat measurement at the Week 104 visit. **Responder:** uPCR <0.5 and eGFR is no more than 10% below pre-flare value or ≥90 mL/min/1.73m^2 and Not a Treatment Failure[a] **Non-Responder:** Not meeting criteria for CRR renal response
PERR at Week 52 Analysed using logistic regression.	PERR at Week 52 was defined in the same manner as PERR at Week 104 only using a response at the Week 48 visit that was confirmed by a repeat measurement at the Week 52 visit to derive the endpoint.
Time to renal-related event or death[b] Analysed using a Cox proportional hazards.	Defined as first of the following: i) Death ii) end stage renal disease (ESRD), iii) doubling of serum creatinine, iv) renal worsening[c] as evidenced by increased proteinuria and/or impaired renal function, or v) renal disease-related treatment failure.
ORR (complete, partial or no response) at Week 104 Analyzed with a rank ANCOVA.	Defined as: - CRR (see definition above) - Partial Renal Response (PRR): eGFR no more than 10% below the baseline value or within normal range and ≥50% decrease in the uPCR with one of the following: a uPCR of <1.0, if the baseline ratio was ≤3.0 OR a uPCR of <3.0, if the baseline ratio was >3.0 AND - Not a treatment failure - No Renal Response (NRR): Not meeting criteria for either CRR or PRR.
Note: If the endpoint specific concurrent medication guidelines described in the protocol were not followed, the subject was to discontinue IP and considered a treatment failure (non-responder) for the respective analysis.	

Endpoint	Definition
a. Treatment failure: Subject who took a protocol-prohibited or restricted medication or dose (see Section 5.5 and Section 5.6 of the protocol with further detail in RAP Section 14.6.3.4). b. In the protocol, RAP and outputs this endpoint is "Time to death or renal-related event". In this report this is referred to as "Time to renal-related event or death" as putting death first is misleading as these were primarily renal-related events. c. Renal worsening is the development of increased proteinuria and/or impaired renal function defined as: Increased Proteinuria (using spot urine); A reproducible increase in 24-hour urine protein levels (as measured in uPCR) to:>1 g if the baseline value was <0.2 g OR >2 g if the baseline value was between 0.2 g and 1 g OR More than twice the value at baseline if the baseline value was >1 g.	

Safety Endpoints: Adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI), Columbia-Suicide Severity Rating Scale (C- SSRS), clinical laboratory parameters, immunogenicity, and vital signs.

Pharmacokinetic (PK) Endpoint: serum belimumab concentrations.

Sample size

The original sample size calculations for ORR resulted in a target sample size of N=464 subjects (232 per arm) in order to achieve at least 85% power to detect a treatment difference for the initial primary endpoint. Recruitment was completed with a final sample size N=448; the primary endpoint was revised to PERR and power was estimated at 80% for response rates of 40% and 53.6%.

Randomisation

Subjects were assigned to study treatment in accordance with the randomization schedule. On Day 1, subjects were assigned to IP by Interactive Voice Response System (IVRS). Subjects were randomized in a 1:1 ratio to treatment with either 10 mg/kg belimumab plus standard of care or placebo plus standard of care. Randomization of all eligible subjects was stratified by their induction regimen (HDCS plus CYC vs HDCS plus MMF) and race (black race vs other). There was race stratification in this study because race may be an important factor related to outcomes in patients with lupus nephritis. Race was to be self-designated.

Blinding (masking)

Belimumab and placebo were supplied as open-label vials; 3rd party unblinding was employed. The investigational product (IP) was reconstituted and diluted by the unblinded site pharmacist or qualified designee, independent of the study (person responsible for receiving and dispensing IP). Except for a limited number of safety oversight personnel, all study site personnel, the subject, the sponsor, and the CROs were blinded to the IP received and to the results of certain biomarker and pharmacodynamic laboratory results. Separate monitors were responsible for the clinical (blinded monitor) and IP (unblinded monitor) aspects of the study. Treatment codes could be unblinded by the investigator or treating physician only in the case of a medical emergency or in the event of a serious medical condition, when knowledge of the study drug was essential for the clinical management or welfare of the subject. The GSK Central Safety Department (CSD, formerly Global Clinical Safety and Pharmacovigilance [GCSP]) staff could unblind treatment codes in the event of a serious adverse event (SAE).

Statistical methods

All statistical models for the primary and major secondary endpoints controlled for induction regimen, race, baseline uPCR, and baseline eGFR. Subjects who met treatment failure (TF) criteria were to continue in the study. For the primary efficacy endpoint and major secondary efficacy endpoints (other than time to renal-related event or death), subjects who discontinued IP or from the study were imputed as non-responders from the visit after the first missed IP dose. For the time to renal-related event or death endpoint, the data was censored from the first missed IP dose.

No interim analyses were planned or performed for this study. The two database locks for this study correspond to the primary analysis (end of double-blind period, this report) and the open-label extension analysis (end of study analysis). All subjects and study site personnel (except the unblinded site pharmacist) were to remain blinded until the open-label extension data was locked.

Analysis populations

Modified Intent-To-Treat (MITT): All randomised participants who received at least one dose of study treatment. This population will be based on the treatment to which the subject was randomised. Excludes the one subject at site 107299 due to GCP non-compliance issues and the one subject at site 107398 due to insufficient source documentation.

Per-Protocol (PP): A subset of the MITT population who comply with the protocol. Protocol deviations that would exclude participants from the PP population are defined in RAP. The PP set will only be analysed if this population excludes more than 15% of the MITT population.

Completers on Study agent: Subjects in the MITT population who completed through Week 104 and were not permanently discontinued from treatment prior to Week 104.

Completers on Study: Subjects in the MITT population who completed through Week 104 including subjects both on and off treatment.

Analysis of primary endpoint

PERR at Week 104 was measured as a dichotomous response (Responder vs Non-Responder). PERR was determined by reproducible changes in proteinuria and renal function. The PERR at Week 104 was defined by a response at the Week 100 visit that was confirmed by a repeat measurement at the Week 104 visit. PERR (Responder vs. Non-Responder) at Week 104 was compared between belimumab and placebo using logistic regression controlling for induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR.

For the primary efficacy analysis several sensitivity/supplementary analyses were performed including a treatment policy analysis, an unadjusted analysis and a completer analysis. In addition, tipping point analyses were performed on the treatment policy and hybrid non-TF Estimands.

Two treatment policy analyses were performed. One analysis, referred to as the Treatment Policy analysis, ignores intercurrent events of IP discontinuation and treatment failure such that all data observed after these events will be used in the analysis. Additionally, a hybrid treatment policy analysis implements the composite strategy for treatment failure since it is a component of the primary endpoint, and a treatment policy strategy for intercurrent events of IP discontinuation. In this hybrid treatment policy analysis, treatment failures are treated as non-responders from the date of treatment failure onward and IP discontinuations are ignored such that all observed data after IP discontinuation is used in the analysis. Missing data due to study withdrawal, loss to follow-up, or death were treated as non-responders from the date of the intercurrent event onward.

Tipping point analyses were performed for the primary endpoint (PERR) and the complete renal response (CRR) endpoint. The tipping point analysis were based on the modified Intent-to-treat population using both the hybrid treatment policy and treatment policy intercurrent event strategies.

Analysis of secondary endpoints

Major secondary efficacy endpoints were Complete Renal Response at Week 104, Primary Efficacy Renal Response (PERR) at Week 52, Time to Renal-related Event or Death, and Ordinal Renal Response at Week 104. CRR at Week 104 and PERR at Week 52 were analysed using logistic regression as described for the primary analysis. Time to renal-related event or death was analysed using a Cox proportional hazards and ORR was analysed with a rank ANCOVA. All four statistical models controlled for induction regimen, race, baseline uPCR, and baseline eGFR.

Control of type I error

The primary and the 4 major secondary efficacy endpoints were evaluated based on a pre-specified step-down sequential testing procedure to control the overall type 1 error rate. With this procedure, the primary and 4 major secondary endpoints were evaluated for statistical significance, as follows:

- PERR at Week 104
- CRR at Week 104
- PERR at Week 52
- Time to Renal Related Event or Death
- ORR at Week 104.

Analyses of other efficacy endpoints were not subject to any multiplicity adjustment.

Results

Participant flow

Table 16. Number of Subjects in the Analysis Populations

Number of Subjects, n (%)	Placebo	Belimumab 10 mg/kg	Total
Screened			797
Randomized Population[a]	224 (50)	224 (50)	448 (100)
Safety[a]	224 (50)	224 (50)	448 (100)
Modified Intent-to-Treat Population[a]	223 (50)	223 (50)	446 (100)
Per Protocol Population[a]	217 (49.9)	218 (50.1)	435 (100)
Modified Completers on Study Agent[a, b]	132 (47.5)	146 (52.5)	278 (100)
Modified Completers on Study[a, c]	169 (47.6)	186 (52.4)	355 (100)
PK[a]	0	224 (100)	224 (100)

a. All percentages are relative to the number of subjects in the Total column.
b. Subjects who completed through Week 104 who were not prematurely discontinued from randomized treatment prior to Week 104.
c. Includes subjects on study through Week 104 who prematurely discontinued randomized treatment.

Table 17. Investigational Product Status and Reasons for Discontinuation of IP (Double-Blind, mITT Population)

Overall, n (%)	Placebo N=223	Belimumab 10 mg/kg N=223	Total N=446
Investigational Product Status			
Completed	132 (59.2)	146 (65.5)	278 (62.3)
Prematurely discontinued	91 (40.8)	77 (34.5)	168 (37.7)
IP Withdrawn by Week 24	31 (13.9)	33 (14.8)	64 (14.3)
Primary Reason[a]			
Adverse event	30 (13.5)	30 (13.5)	60 (13.5)
Lack of efficacy	20 (9.0)	18 (8.1)	38 (8.5)
Subject met protocol-defined stopping criteria	22 (9.9)	12 (5.4)	34 (7.6)
Decision by subject	13 (5.8)	11 (4.9)	24 (5.4)

a. Subjects may have only one primary reason.

Recruitment

The first subject was enrolled on 12 July 2012, and the last visit in the double-blind phase occurred on 25 July 2019. The open label extension portion of the study was ongoing at the time of variation submission. Final report was submitted during the procedure.

Conduct of the study

Protocol amendments

There were 6 global amendments and 6 local (country specific) amendments to the original protocol (dated 19 Oct 2011). Global Protocol Amendment 07 was used to prepare this CSR. A brief summary of the most important protocol amendments is provided below.

Amendment 01

The protocol was modified to clarify exclusion criteria, concurrent medications and standard of care, addition of anti-malarials, and use of corticosteroids.

There were also changes to prohibited medications and non-drug therapies, live vaccines, screening procedures, and the double-blind treatment period and study calendar. An open-label extension replaced the continuation phase. An exploratory analysis of urinary biomarkers related to lupus nephritis was added. Clarifications were made to the withdrawal of study treatment and adverse event reporting sections. The endpoints and statistical analysis sections were updated to reflect changes made in other sections of the protocol.

Amendment 02

Language describing subject unblinding in the protocol was amended. Language regarding the body weight used for dose calculation was corrected.

Amendment 03

The protocol was modified to expand Hepatitis B serology testing, and to exclude patients who tested positive according to the criteria specified, and to specify hepatitis C screening test by HCV RNA-PCR assay with additional wording to further clarify subject eligibility.

The Screening window was extended from 28 days to 35 days and the Induction initiation window has been extended from 14 days to 21 days to improve the feasibility of subject identification.

The exclusion criteria were modified to exclude subjects treated with interleukin-6 targeted therapy within 364 days of baseline, to clarify that Grade 3 laboratory abnormalities include serum IgG level, and "Hyperuricemia or blood urea nitrogen (BUN) elevation due to lupus nephritis or SLE" was added to the list of Grade 3 or greater laboratory abnormalities allowed.

In addition, clarification was added for screening for active or latent infections. The concurrent medication section was modified. Steroid rescue for non-renal SLE disease activity and non-SLE disease activity was revised. Measurement of vital signs and a 12-lead electrocardiogram (ECG) were added. Timing of pharmacokinetic sampling in subjects who withdrew from the study was clarified. A new section was added to clarify management of patients with liver chemistry events during the study. Reason for treatment withdrawal was modified to include "Missing 3 or more consecutive doses of study drug". Subject unblinding information was updated.

Amendment 05

The eligibility criteria were modified to allow patients who initiated an induction most recently and have continued, to be considered for enrollment. The slight expansion of the induction initiation window up to 60 days prior to Day 1 was unlikely to confound the primary efficacy evaluation because patients will only have been on SoC induction for a short period before enrolment and their disease is still highly active at baseline. Relevant sections were modified accordingly.

Local Amendment 05 (France (1))

In addition to the changes described above for Amendment 05 for all sites, at the request of the French National Agency for Medicines and Health Products Safety (ANSM), the protocol was revised to include guidance for French investigators to evaluate suspected cases of PML using brain imaging and polymerase chain reaction (PCR) on cerebrospinal fluid for JC virus (JCV).

Local Amendment 05 (France (2))

The Local Amendment 05 (2) for France was implemented on 13 July 2016 and applied only in France. In addition to the changes described above for Amendment 05 (1), at the request of the ANSM, the protocol was modified to comply with the information updated in November 2015 in the Cellcept Summary of Product Characteristics (SPC) and package leaflet reflecting changes to pregnancy test and contraception requirements requirements for women of childbearing potential receiving MMF or Mycophenolate sodium.

Amendment 06 (all countries and sites except for France).

The Local Amendment 06 for France was implemented on 26 Apr 2017 and applied only in France. It contains the same global protocol changes described here in a separate protocol amendment created for specifically for use in France.

The Renal Response definition used for key efficacy endpoints evaluation was modified to remove the urinary sediment component. This change was driven by the latest medical practice suggesting that urinary sediment level is not an appropriate measure for disease change in lupus nephritis as reported in the recent publications on the long-term predictors of renal outcomes in patients with lupus nephritis and the sponsor's experience in urinalysis data collection in a multicenter trial setting.

Calculated GFR based on 24-hour urine collections used in the Complete Renal Response definition was changed to estimated GFR to minimize bias due to sample collection errors. Estimated GFR will be used for all renal function evaluations including the primary and major secondary endpoints.

Time to first renal flare was added as a major secondary efficacy endpoint to support the clinical interpretation of the primary endpoint and to provide additional clinically meaningful evidence. It was placed third in the testing hierarchy after the primary endpoint of renal response and the first major secondary endpoint of complete renal response at Week 104.

In addition, clarification was added regarding timing of the renal biopsy; other relevant sections/text have been modified accordingly. In the Study Design and Statistical analysis sections, language was added allowing for a reduction in sample from the original N=464 due to recruitment difficulties and the timeline for fulfilling the PAC. The recruitment would be curtailed by July 2018 if at least 400 subjects were randomized. There was a sample size sensitivity added to provide context to power at various sample sizes. Contraception requirements were updated. The GFR calculation was corrected to include "/1.73m2". The Benefit-Risk section text was updated in line with current belimumab safety information. The concomitant medications section was updated to clarify concurrent medication rules applicable to the double-blind period. Laboratory text section was updated with the most recent simplified Modification of Diet in Renal Disease [MDRD] equation for estimation of GFR. In the Statistical analysis section, the Van Elteren test was replaced with a Rank analysis of covariance (ANCOVA) for the primary and major secondary endpoints analysis. Updates were also made to how missing values will be handled, how the sensitivity analyses will be performed, and additional other efficacy endpoints were defined. The rate of renal flare from Week 24, time to first renal flare from Week 52, and the rate of renal flare from Week 52 were also added as other efficacy endpoints and for some of the other efficacy endpoints, clarification text has been added.

Amendment 07 (all countries and sites, except for France), 24 January 2019.

The Local Amendment 07 for France was implemented on 18 Feb 2019 and applied only in France. The same global protocol changes described here were summarized in a separate protocol amendment and applied to sites in France. In this amendment, the primary endpoint definition was changed from an ordinal renal response endpoint (complete, partial, no response) to a binary endpoint (responder, non-responder) referred to as PERR. The PERR endpoint is more easily interpretable, is clinically relevant, and has reasonable power to detect a treatment effect. The Time to renal flare at Week 24 endpoint was changed to time to death or renal-related event (now referred to as renal-related event or death). The revised endpoint is more inclusive of events that reflect worsening of renal disease and counting events from initiation of randomized therapy onward. The testing hierarchy was updated to reflect the clinical relevance of the endpoints and statistical power estimations. The analysis methodology of the major secondary endpoints was changed to control for baseline proteinuria and estimated GFR as the endpoints are dependent on changes in these parameters. Power calculations were added to the sample size section to provide estimates for the PERR endpoint given the randomized sample. In addition, the Study Design schematic was updated for the changes to the primary and major secondary endpoints. A subgroup for baseline renal biopsy class was added. Other efficacy endpoints were updated to be consistent with and supportive of the revised testing hierarchy. Endpoints inadvertently omitted were added to other efficacy endpoints. The timeframe for pregnancy reporting was updated to sponsor requirements.

Protocol deviations

Important deviations included, but were not limited to, those related to study inclusion or exclusion criteria, adherence to the protocol, conduct of the study, violation of GCP principles, subject management or subject assessment. The percentage of subjects with important protocol deviations in the mITT population was similar between the placebo and belimumab groups (51.6% and 48.9%, respectively, Table 18). In both treatment groups, the largest proportion of important protocol deviations was in the

category of assessments and/or procedures. This broad category included deviations related to the informed consent process, failure to comply with required safety assessments, missed assessments or procedures, and study treatment supply procedures. Most of the informed consent deviations were due to delay in timing of re-consenting for ICF revisions and there were no specific patterns for the subcategory of other deviations.

Table 18. Subjects with Important Protocol Deviations (Double-Blind, mITT Population)

Deviation Subcategory	Number (%) of Subjects		
	Placebo (N=223)	Belimumab 10 mg/kg (N=223)	Total (N=446)
Any important protocol deviations[a]	115 (51.6)	109 (48.9)	224 (50.2)
Eligibility criteria not met	18 (8.1)	13 (5.8)	31 (7.0)
Not withdrawn after developing withdrawal criteria	29 (13.0)	26 (11.7)	55 (12.3)
Received wrong treatment or incorrect dose	8 (3.6)	3 (1.3)	11 (2.5)
Assessments and/or procedures	92 (41.3)	86 (38.6)	178 (39.9)
Informed consent process	38 (17.0)	36 (16.1)	74 (16.6)
Failure to report SAE, pregnancy, or liver function abnormality	18 (8.1)	13 (5.8)	31 (7.0)
Study treatment supply procedures	12 (5.4)	8 (3.6)	20 (4.5)
Biological sample specimen procedures	2 (0.9)	0	2 (0.4)
Randomization procedures	1 (0.4)	3 (1.3)	4 (0.9)
Missed assessment or procedure-other	9 (4.0)	12 (5.4)	21 (4.7)
Other	49 (22.0)	52 (23.3)	101 (22.6)
Other protocol deviation category	12 (5.4)	10 (4.5)	22 (4.9)

a. Subjects may have been included in more than 1 category.

GCP noncompliance

Due to GCP noncompliance issues, subjects who had at least one assessment at site 107299 in the US and site 107398 in the Philippines were excluded from the mITT population; 2 subjects (1 at each site) were impacted and data from these 2 subjects were excluded from all efficacy analyses, but were included in the safety analyses.

Baseline data

Overall demographic characteristics are presented in Table 19.

Table 19. Demographic and Baseline Characteristics (Double-Blind; mITT Population)

Overall	Placebo N=223	Belimumab 10 mg/kg N=223	Total N=446
Region,n (%)			
Asia	105 (47.1)	106 (47.5)	211 (47.3)
Europe	45 (20.2)	41 (18.4)	86 (19.3)
US/Canada	38 (17.0)	38 (17.0)	76 (17.0)
Americas excluding US/Canada	35 (15.7)	38 (17.0)	73 (16.4)
Sex, n (%)			
Female	196 (87.9)	197 (88.3)	393 (88.1)
Male	27 (12.1)	26 (11.7)	53 (11.9)
Ethnicity, n (%)			
Hispanic or Latino	43 (19.3)	50 (22.4)	93 (20.9)
Not Hispanic or Latino	180 (80.7)	173 (77.6)	353 (79.1)
Age (years), n	223	223	446
Mean (SD)	33.1 (10.64)	33.7 (10.74)	33.4 (10.68)
Median	31.0	31.0	31.0
Min, Max	18, 77	18, 63	18, 77
Age Group (years), n (%)	223	223	446
<=45	190 (85.2)	191 (85.7)	381 (85.4)
> 45 to < 65	31 (13.9)	32 (14.3)	63 (14.1)
>= 65	2 (0.9)	0	2 (0.4)
>= 65 - 75	1 (0.4)	0	1 (0.2)
>= 75	1 (0.4)	0	1 (0.2)
Race [a], n (%)	223	223	446
American Indian or Alaskan Native	6 (2.7)	4 (1.8)	10 (2.2)
Asian	109 (48.9)	114 (51.1)	223 (50.0)
Black or African American	31 (13.9)	30 (13.5)	61 (13.7)
White/Caucasian	75 (33.6)	73 (32.7)	148 (33.2)
Multiple	2 (0.9)	2 (0.9)	4 (0.9)
BMI (kg/m²), n	223	223	446
Mean (SD)	24.496 (5.5652)	23.841 (4.6991)	24.169 (5.1550)
(Min, Max)	14.91, 51.25	16.05, 45.74	14.91, 51.25

a. Subjects are only counted in one category.

Baseline disease activity is presented overall in Table 20.

Table 20. Baseline Disease Characteristics (Double-Blind; mITT Population)

Overall	Placebo N=223	Belimumab 10 mg/kg N=223	Total N=446
SLE Disease duration (years) [a], n	223	223	446
Mean (SD)	5.14 (5.781)	5.49 (6.415)	5.32 (6.102)
Median (IQR)	3.26 (0.22, 7.99)	3.27 (0.30, 8.14)	3.27 (0.24, 8.11)
LN Disease duration (years) [a], n	223	223	446
Mean (SD)	2.35 (4.140)	2.28 (4.264)	2.31 (4.198)
Median (IQR)	0.18 (0.10, 3.35)	0.19 (0.09, 3.30)	0.18 (0.10, 3.31)
Renal Biopsy Class[b] Local Reader, n (%)	223	223	446
Class III (A)	26 (11.7)	25 (11.2)	51 (11.4)
Class III (A/C)	46 (20.6)	43 (19.3)	89 (20.0)
Class IV-S (A)	23 (10.3)	12 (5.4)	35 (7.8)
Class IV-G (A)	40 (17.9)	41 (18.4)	81 (18.2)
Class IV-S (A/C)	15 (6.7)	21 (9.4)	36 (8.1)
Class IV-G (A/C)	37 (16.6)	46 (20.6)	83 (18.6)
Class V	91 (40.8)	97 (43.5)	188 (42.2)
Renal Biopsy Class Category[c] Local Reader, n (%)	223	223	446
Class III or IV	132 (59.2)	126 (56.5)	258 (57.8)
Class III+V or Class IV+V	55 (24.7)	61 (27.4)	116 (26.0)
Class V	36 (16.1)	36 (16.1)	72 (16.1)
Renal Biopsy Class[b] Central Reader[d], n (%)	160	155	315
Class I	0	1 (0.6)	1 (0.3)
Class II	4 (2.5)	1 (0.6)	5 (1.6)
Class III (A)	22 (13.8)	20 (12.9)	42 (13.3)
Class III (A/C)	22 (13.8)	19 (12.3)	41 (13.0)
Class III (C)	3 (1.9)	1 (0.6)	4 (1.3)
Class IV-S (A)	20 (12.5)	27 (17.4)	47 (14.9)
Class IV-G (A)	25 (15.6)	17 (11.0)	42 (13.3)
Class IV-S (A/C)	34 (21.3)	27 (17.4)	61 (19.4)
Class IV-G (A/C)	16 (10.0)	22 (14.2)	38 (12.1)
Class IV-S (C)	1 (0.6)	1 (0.6)	2 (0.6)
Class IV-G (C)	1 (0.6)	1 (0.6)	2 (0.6)
Class V	43 (26.9)	51 (32.9)	94 (29.8)
Renal Biopsy Class Category[c] Central Reader[d], n (%)	160	155	315
Class III or IV	113 (70.6)	102 (65.8)	215 (68.3)
Class III+V or Class IV+V	30 (18.8)	33 (21.3)	63 (20.0)
Class V	13 (8.1)	18 (11.6)	31 (9.8)
Other	4 (2.5)	2 (1.3)	6 (1.9)
Urine Protein-Creatinine Category (g/g), n (%)			
<0.5	8 (3.6)	9 (4.0)	17 (3.8)
0.5 - <3	123 (55.2)	123 (55.2)	246 (55.2)
>=3	92 (41.3)	91 (40.8)	183 (41.0)
<=0.7	15 (6.7)	22 (9.9)	37 (8.3)

Overall	Placebo N=223	Belimumab 10 mg/kg N=223	Total N=446
Urine Protein-Creatinine Ratio Level (g/g), n	223	223	446
Mean (SD)	3.5291 (3.56148)	3.1982 (2.74559)	3.3636 (3.18055)
Median (IQR)	2.4720 (1.3540, 4.8080)	2.6060 (1.1240, 4.3620)	2.4980 (1.2470, 4.6000)
Estimated GFR (mL/min/1.73m²) Category			
<30	6 (2.7)	3 (1.3)	9 (2.0)
30 - <60	35 (15.7)	30 (13.5)	65 (14.6)
60 - <90	49 (22.0)	59 (26.5)	108 (24.2)
>=60	182 (81.6)	190 (85.2)	372 (83.4)
>=90	133 (59.6)	131 (58.7)	264 (59.2)
Estimated GFR (mL/min/1.73m²), n	223	223	446
Mean (SD)	101.0 (42.70)	100.0 (37.71)	100.5 (40.24)
Median (IQR)	98.0 (67.0, 127.0)	99.0 (72.0, 124.0)	98.5 (70.0, 125.0)
SLEDAI-S2K category, n (%)			
<8	36 (16.1)	37 (16.6)	73 (16.4)
8-<12	60 (26.9)	55 (24.7)	115 (25.8)
12-<16	59 (26.5)	63 (28.3)	122 (27.4)
≥16	67 (30.0)	68 (30.5)	135 (30.3)
Missing	1 (0.4)	0	1 (0.2)
SLEDAI-S2K score, n	222	223	445
Mean (SD)	12.2 (4.81)	12.5 (5.26)	12.3 (5.03)
Median (IQR)	12.0 (8.0, 16.0)	12.0(8.0, 16.0)	12.0 (8.0, 16.0)
PGA category, n (%)			
0 – 1	25 (11.2)	24 (10.8)	49 (11.0)
>1 – 2.5	174 (78.0)	173 (77.6)	347 (77.8)
>2.5	22 (9.9)	18 (8.1)	40 (9.0)
Missing	2 (0.9)	8 (3.6)	10 (2.2)
PGA, n	221	215	436
Mean (SD)	1.771 (0.6001)	1.779 (0.5896)	1.775 (0.5943)
Median (IQR)	1.860 (1.320, 2.250)	1.860 (1.380, 2.190)	1.860 (1.365, 2.220)
SLICC category			
0	164 (73.5)	171 (76.7)	335 (75.1)
1	44 (19.7)	34 (15.2)	78 (17.5)
>1	15 (6.7)	17 (7.6)	32 (7.2)
Missing	0	1 (0.4)	1 (0.2)
SLICC Damage Index score, n	223	222	445
Mean (SD)	0.4 (0.82)	0.4 (1.11)	0.4 (0.97)
Median (Min, Max)	0 (0, 6)	0 (0, 11)	0 (0, 11)

a. Duration defined as (Screening date - Diagnosis date + 1)/365.25.
b. Subjects may be in more than one category.
c. Based on the presence of Class III, IV, and V results although other classes may be present also.
d. Not all subjects had an assessment by the central reader.

Lupus nephritis therapy history prior to enrollment in the study is presented overall in Table 21.

Table 21. Lupus Nephritis Therapy History (Double-Blind; mITT Population)

	Placebo N=223	Belimumab 10 mg/kg N=223	Total N=446
Previous Cyclophosphamide Therapy?, n	223	223	446
No, n (%)	176 (78.9)	180 (80.7)	356 (79.8)
Yes, n (%)	47 (21.1)	43 (19.3)	90 (20.2)
Subject Responded to Therapy	41 (18.4)	31 (13.9)	72 (16.1)
Subject Failed Therapy	6 (2.7)	11 (4.9)	17 (3.8)
Missing	0	1 (0.4)	1 (0.2)
Previous Mycophenolate[a] Therapy?, n	223	223	446
No, n (%)	189 (84.8)	192 (86.1)	381 (85.4)
Yes, n (%)	34 (15.2)	31 (13.9)	65 (14.6)
Subject Responded to Therapy	26 (11.7)	19 (8.5)	45 (10.1)
Subject Failed Therapy	8 (3.6)	12 (5.4)	20 (4.5)

a. Mycophenolate mofetil or any other form of mycophenolate.

Disease characteristics forming the ACR classification of SLE are presented overall in Table 22.

Table 22. ACR SLE Classification Criteria at Baseline (Double-Blind; mITT Population)

	Number (%) of Subjects		
	Placebo N=223	Belimumab 10 mg/kg N=223	Total N=446
ACR Classification Criteria [a]	223	223	446
Malar "butterfly" rash	129 (57.8)	130 (58.3)	259 (58.1)
Discoid rash	42 (18.8)	36 (16.1)	78 (17.5)
Photosensitivity	95 (42.6)	89 (39.9)	184 (41.3)
Oral ulcers	71 (31.8)	75 (33.6)	146 (32.7)
Arthritis	138 (61.9)	163 (73.1)	301 (67.5)
Serositis	48 (21.5)	43 (19.3)	91 (20.4)
Pleuritis	34 (15.2)	35 (15.7)	69 (15.5)
Pericarditis	30 (13.5)	23 (10.3)	53 (11.9)
Renal Disorder	223 (100)	223 (100)	446 (100)
Persistent Proteinuria	222 (99.6)	220 (98.7)	442 (99.1)
Cellular Casts	61 (27.4)	52 (23.3)	113 (25.3)
Neurologic Disorder	7 (3.1)	2 (0.9)	9 (2.0)
Seizures	2 (0.9)	1 (0.4)	3 (0.7)
Psychosis	3 (1.3)	0	3 (0.7)
Hematologic Disorder	122 (54.7)	110 (49.3)	232 (52.0)
Hemolytic Anemia	31 (13.9)	32 (14.3)	63 (14.1)
Leukopenia	77 (34.5)	64 (28.7)	141 (31.6)
Lymphopenia	69 (30.9)	60 (26.9)	129 (28.9)
Thrombocytopenia	25 (11.2)	26 (11.7)	51 (11.4)
Immunologic disorder	206 (92.4)	208 (93.3)	414 (92.8)
Anti-DNA	196 (87.9)	192 (86.1)	388 (87.0)
Anti-Sm	51 (22.9)	65 (29.1)	116 (26.0)
Antiphospholipid Antibodies	24 (10.8)	25 (11.2)	49 (11.0)
ANA	216 (96.9)	212 (95.1)	428 (96.0)

a. SLE was diagnosed when any 4 or more entry criteria were present, serially or simultaneously.

The randomization of all eligible subjects was stratified by their induction/maintenance regimen (HDCS plus CYC followed by AZA vs HDCS plus MMF followed by MMF) and race (black race vs other) (Table 23).

Table 23. Stratification Factors at Baseline (Double-Blind; mITT Population)

	Number (%) of Subjects		
	Placebo N=223	Belimumab 10 mg/kg N=223	Total N=446
Number of Subjects in Induction Regimen, n	223	223	446
Induction/Maintenance Regimen			
CYC/AZA	59 (26.5)	59 (26.5)	118 (26.5)
MMF	164 (73.5)	164 (73.5)	328 (73.5)
Race			
Black	32 (14.3)	31 (13.9)	63 (14.1)
Non-Black	191 (85.7)	192 (86.1)	383 (85.9)
Induction/Maintenance Regimen and Race Strata			
CYC/AZA and Black	10 (4.5)	9 (4.0)	19 (4.3)
CYC/AZA and Non-Black	49 (22.0)	50 (22.4)	99 (22.2)
MMF and Black	22 (9.9)	22 (9.9)	44 (9.9)
MMF and Non-Black	142 (63.7)	142 (63.7)	284 (63.7)

Note: Based on data collected in the eCRF.

The number and percentage of subjects taking each category of allowable SLE and LN medications is presented below.

Table 24. Allowable SLE and LN Medication Usage at Baseline (Double-Blind; mITT Population)

	Placebo N= 223	Belimumab 10 mg/kg N= 223	Total N= 446
Average Daily Prednisone [a] Dose (mg/day)			
Mean (SD)	72.52 (133.162)	66.50 (99.591)	69.51 (117.487)
Median (25th, 75th percentile)	45.00 (30.00, 60.00)	50.00 (30.00, 60.00)	50.00 (30.00, 60.00)
Number (%) of Subjects Taking			
Steroids	210 (94.2)	216 (96.9)	426 (95.5)
Antimalarials	154 (69.1)	166 (74.4)	320 (71.7)
Immunosuppressants	192 (86.1)	198 (88.8)	390 (87.4)
ACEi/ARBs [b]	150 (67.3)	147 (65.9)	297 (66.6)

a. Steroids were converted to prednisone equivalent.
b. Angiotensin-converting enzyme (ACE) inhibitors / angiotensin receptor antagonists/blockers (ARBs)

Numbers analysed

The numbers of subjects in the analysis populations are summarized below. The mITT population is a subset of the Safety population with the exclusion of 2 subjects from the 2 sites previously described. No Per-Protocol Population analysis was performed as the number of subjects excluded was <15%.

Table 25. Number of Subjects in the Analysis Populations

Number of Subjects, n (%)	Placebo	Belimumab 10 mg/kg	Total
Screened			797
Randomized Population[a]	224 (50)	224 (50)	448 (100)
Safety[a]	224 (50)	224 (50)	448 (100)
Modified Intent-to-Treat Population[a]	223 (50)	223 (50)	446 (100)
Per Protocol Population[a]	217 (49.9)	218 (50.1)	435 (100)
Modified Completers on Study Agent[a, b]	132 (47.5)	146 (52.5)	278 (100)
Modified Completers on Study[a, c]	169 (47.6)	186 (52.4)	355 (100)
PK[a]	0	224 (100)	224 (100)

a. All percentages are relative to the number of subjects in the Total column.
b. Subjects who completed through Week 104 who were not prematurely discontinued from randomized treatment prior to Week 104.
c. Includes subjects on study through Week 104 who prematurely discontinued randomized treatment.

Outcomes and estimation

Results for the **primary and major secondary endpoints** are shown in Table 26.

Table 26. Primary and Major Secondary Efficacy Summary Table (Double-Blind, mITT)

Efficacy Endpoint	n (%) Placebo N=223	n (%) Belimumab 10 mg/kg N=223	Observed difference (%) vs. placebo	Odds/Hazard ratio (95% CI) [a] vs. placebo	p-value [a]	Results Section
PRIMARY:						
PERR at Week 104, Responders	72 (32.3)	96 (43.0)	10.76	OR=1.55 (1.04, 2.32)	0.0311	Section 6.1
MAJOR SECONDARY:						
CRR at Week 104 [b] Responders	44 (19.7)	67 (30.0)	10.31	OR=1.74 (1.11, 2.74)	0.0167	Section 6.2.1
PERR at Week 52 Responders	79 (35.4)	104 (46.6)	11.21	OR=1.59 (1.06, 2.38)	0.0245	Section 6.2.2
Time to Renal-Related Event or Death [c] Subjects with an Event	63 (28.3)	35 (15.7)	-	HR=0.51 (0.34, 0.77)	0.0014	Section 6.2.3
Ordinal Renal Response at Week 104 [b] Complete Renal Responders	44 (19.7)	67 (30.0)	10.31	-	0.0096	Section 6.2.4
Partial Renal Responders	38 (17.0)	39 (17.5)	0.45	-		
Non-Responders	141 (63.2)	117 (52.5)	-10.76	-		

OR=Odds Ratio, HR=Hazard Ratio

a. Odds Ratio (95% confidence interval) and p-value are from a logistic regression model for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR. Hazard ratio and p-value are from Cox proportional hazards model for the comparison between Belimumab and Placebo adjusting for induction regimen, race, baseline uPCR, and baseline eGFR.

b. Study Withdrawal (WD), Treatment Failures (TF) and Investigational Product Discontinuation (IPD) imputed as non-responders. IPD/TF not related to renal disease/WD are censored in the time to event analysis.

c. Events are defined as the first event experienced among the following: death, progression to end stage renal disease, doubling of serum creatinine from baseline, renal worsening, or renal-related treatment failure. Subjects who discontinue randomized treatment, withdraw from the study, or are lost to follow-up are censored on the date. Subjects who complete the 104-week treatment period are censored at the Week 104 visit. Time to event is defined as (event date - treatment start date + 1).

Primary endpoint – PERR at week 104

The PERR (Responder vs. Non-Responder) at Week 104 was compared between the belimumab and placebo groups using a logistic regression model controlling for induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR. Baseline proteinuria, race, and treatment group were statistically significant predictors of response in the model with higher levels of proteinuria and black race predicted lower overall response rate.

Week 104 analyses for the 3 components of PERR (uPCR, eGFR, not a TF at Week 104) are presented below.

Table 27. PERR Components at Week 104 (IPD/TF/WD=NR) (Double-Blind, mITT Population)

PERR Component		Placebo N=223	Belimumab 10 mg/kg N=223
Urine protein:creatinine ratio ≤0.7	n	223	223
	Responders, n (%)	75 (33.6)	99 (44.4)
	SE % Responders	3.16	3.33
	Observed difference vs. placebo		10.76%
	CMH Adjusted[a] difference vs. Placebo		10.70%
	CMH Adjusted[a] (95% CI) vs. Placebo		(1.79, 19.61)
	Odds ratio (95% CI)[b] vs. placebo		1.54 (1.04, 2.29)
	p-value[b]		0.0320
eGFR no more than 20% below pre-flare value or ≥60mL/min/1.73m²	n	223	223
	Responders, n (%)	112 (50.2)	128 (57.4)
	SE % Responders	3.35	3.31
	Observed difference vs. placebo		7.17%
	CMH Adjusted[a] difference vs. Placebo		7.10%
	CMH Adjusted[a] (95% CI) vs. Placebo		(-1.84, 16.04)
	Odds ratio (95% CI)[b] vs. placebo		1.32 (0.90, 1.94)
	p-value[b]		0.1599
Not a Treatment Failure	n	223	223
	Responders, n (%)	166 (74.4)	185 (83.0)
	SE % Responders	2.92	2.52
	Observed difference vs. placebo		8.52%
	CMH Adjusted[a] difference vs. Placebo		8.49%
	CMH Adjusted[a] (95% CI) vs. Placebo		(1.06, 15.93)
	Odds ratio (95% CI)[b] vs. placebo		1.65 (1.03, 2.63)
	p-value[b]		0.0364

a. Cochran-Mantel-Haenszel estimates are adjusted for induction regimen (CYC vs. MMF) and race (Black vs. Non-Black).
b. Odds Ratio (95% confidence interval) and p-value are from a logistic regression model for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR.

PERR over time

The proportion of subjects meeting criteria for PERR is presented by visit for the overall mITT population in Figure 19. A numerically greater percentage of subjects in the belimumab group than in the placebo group achieved PERR beginning at Week 24 and this was maintained through Week 104.

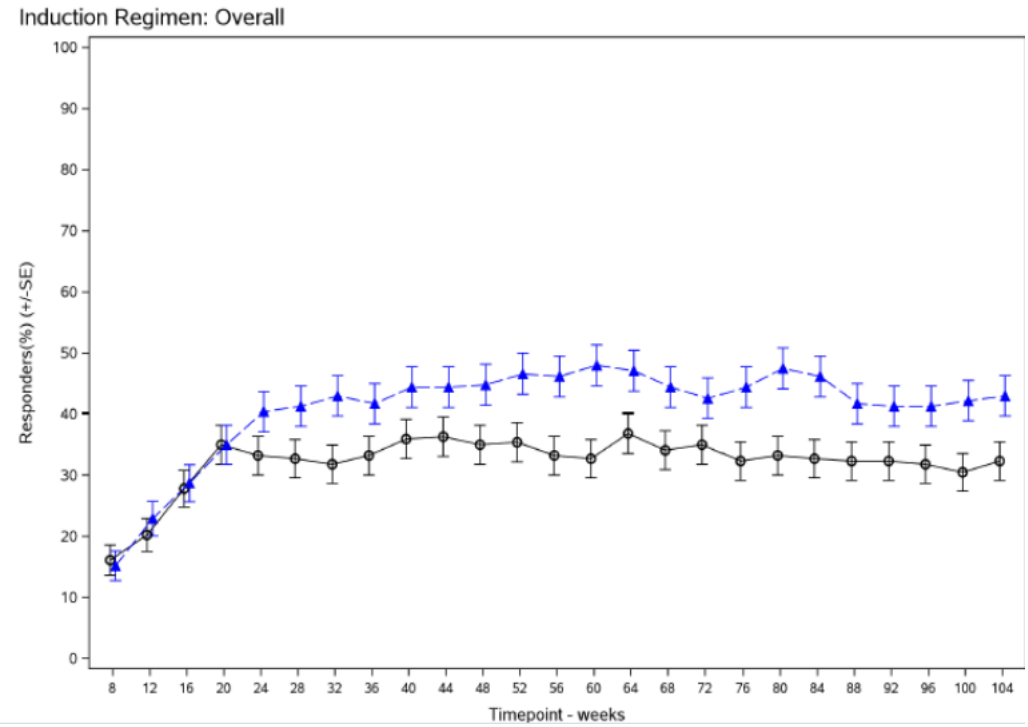


Figure 19. PERR by Visit (IPD/TF/WD=NR) (Double-Blind, mITT Population)

Major secondary endpoints

Complete renal response

Results for CRR is shown in Table 26. The components of CRR are shown in the table below.

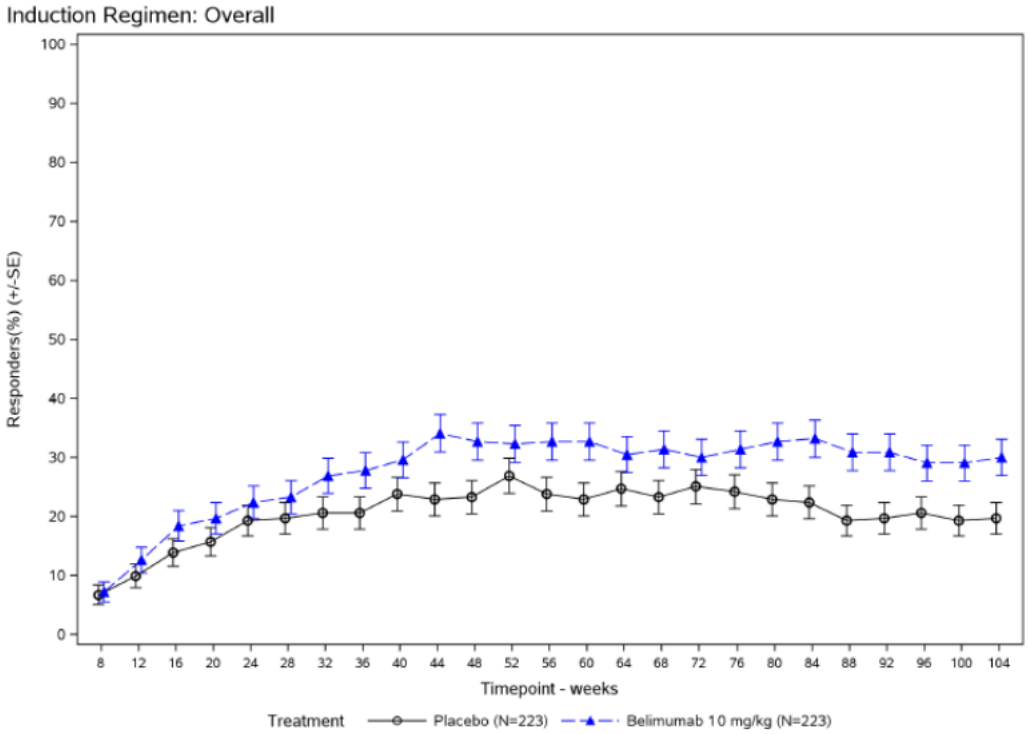
Table 28. The 3 Components of CRR at Week 104 (IPD/TF/WD=NR) (Double-Blind, mITT Population)

Week 104 CRR Component		Placebo N=223	Belimumab 10 mg/kg N=223
Urine protein:creatinine ratio < 0.5	n	223	223
	Responders, n (%)	64 (28.7)	88 (39.5)
	SE % Responders	3.03	3.27
	Observed difference vs. placebo	-	10.76%
	CMH Adjusted[a] difference vs. Placebo	-	10.72%
	CMH Adjusted[a] (95% CI) vs. Placebo	-	(2.04, 19.40)
	Odds ratio (95% CI)[b] vs. placebo	-	1.58 (1.05, 2.38)
	p-value[b]	-	0.0268
eGFR no more than 10% below pre-flare value or within the normal range	n	223	223
	Responders, n (%)	89 (39.9)	104 (46.6)
	SE % Responders	3.28	3.34
	Observed difference vs. placebo	-	6.73%
	CMH Adjusted[a] difference vs. Placebo	-	6.68%
	CMH Adjusted[a] (95% CI) vs. Placebo	-	(-2.31, 15.67)
	Odds ratio (95% CI)[b] vs. placebo	-	1.33 (0.90, 1.96)
	p-value[b]		0.1539
Not a Treatment Failure	n	223	223
	Responders, n (%)	166 (74.4)	185 (83.0)
	SE % Responders	2.92	2.52
	Observed difference vs. placebo	-	8.52%
	CMH Adjusted[a] difference vs. Placebo	-	8.49%
	CMH Adjusted[a] (95% CI) vs. Placebo	-	(1.06, 15.93)
	Odds ratio (95% CI)[b] vs. placebo	-	1.65 (1.03, 2.63)
	p-value[b]	-	0.0364

a. Cochran-Mantel-Haenszel estimates are adjusted for induction regimen (CYC vs. MMF) and race (Black vs. Non-Black).
b. Odds Ratio (95% confidence interval) and p-value are from a logistic regression model for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR.

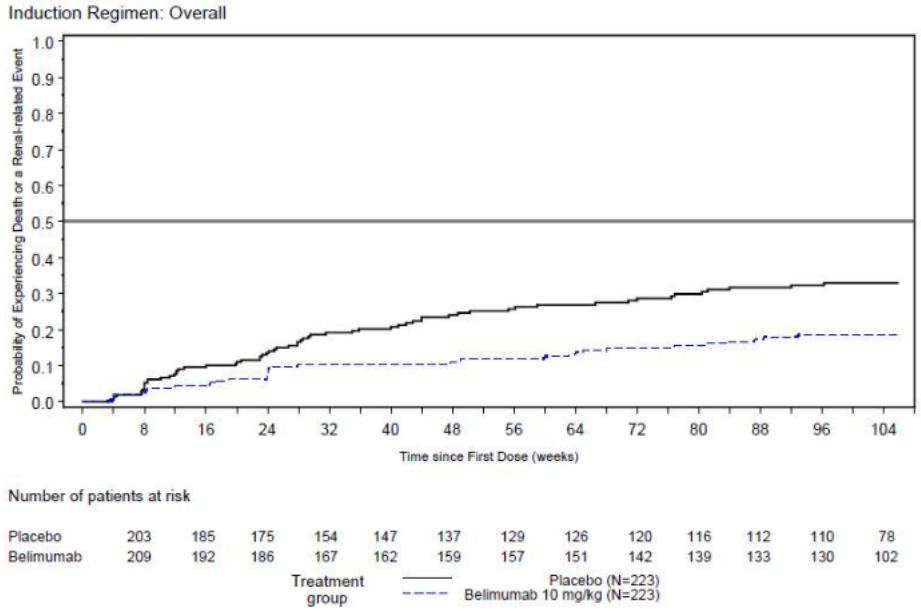
CRR over time

A numerically higher percentage of subjects achieved CRR in the belimumab group than in the placebo group at each visit and maintained through Week 104.



Time to renal-related event or death

Time to renal-related event or death is a composite endpoint defined as the first event occurring after Day 1 among the following: 1) death, 2) ESRD, 3) doubling of serum creatinine, 4) renal worsening as evidenced by increased proteinuria and/or impaired renal function, or 5) renal disease-related treatment failure. Figure 20 shows the probability of experiencing a renal-related event over time or death. The risk of a renal-related event or death at any time up to Week 104 was 49% less in the belimumab group than in the placebo group (HR=0.51; 95% CI: 0.34, 0.77; p=0.0014). The percentage of subjects with a renal-related event or death was 15.7% in the belimumab group and 28.3% in the placebo group. Among those subjects who experienced a renal-related event or death, the median study day to event was 170 for the belimumab group and 188 for the placebo group.



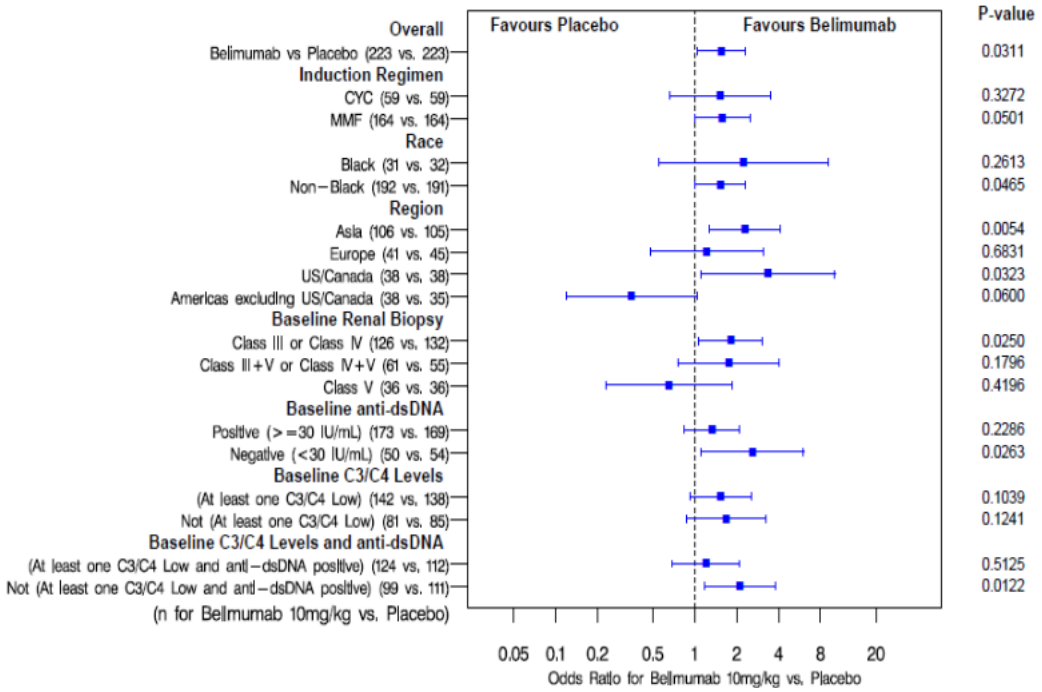
Source: Figure 2.21
The at risk numbers are the number of subjects who have the potential to experience the event at that timepoint.
Figure is truncated at Day 742.

Figure 20. Time to Renal-related Event or Death (IPD/TF not related to renal disease/WD=Censor) (Double-blind, mITT Population

Efficacy in pre-defined subgroups

Primary endpoint, PERR

Results of the PERR at Week 104 for the pre-defined subgroup analyses are provided below.



Selected subgroups are presented in more detail below.

Region

Table 29. PERR at Week 104 By Region (IPD/TF/WD=NR) (Double-Blind, mITT Population)

Region Subgroup	Placebo N=223	BEL N=223
Asia, n	105	106
Responders, n (%)	31 (29.5)	54 (50.9)
SE %Responders	4.45	4.86
Observed difference vs. placebo	-	21.42
Odds ratio (95% CI) vs. placebo	-	2.29 (1.28, 4.10)
p-value	-	0.0054
Europe, n	45	41
Responders, n (%)	15 (33.3)	15 (36.6)
SE %Responders	7.03	7.52
Observed difference vs. placebo	-	3.25
Odds ratio (95% CI) vs. placebo	-	1.22 (0.48, 3.10)
p-value	-	0.6831
US/Canada, n	38	38
Responders, n (%)	9 (23.7)	16 (42.1)
SE %Responders	6.90	8.01
Observed difference vs. placebo	-	18.42
Odds ratio (95% CI) vs. placebo	-	3.36 (1.11, 10.19)
p-value	-	0.0323
Americas excluding US/Canada, n	35	38
Responders, n (%)	17 (48.6)	11 (28.9)
SE %Responders	8.45	7.36
Observed difference vs. placebo	-	-19.62
Odds ratio (95% CI) vs. placebo	-	0.35 (0.12, 1.04)
p-value	-	0.0600
Interaction Test p-value	-	0.0190

Odds Ratio (OR), 95% confidence interval (CI), and p-value are from a logistic regression model run within the subgroup level for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR. Interaction p-value is from a logistic regression model for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, baseline eGFR, region (Asia, Europe, US/Canada, Americas excluding US/Canada), and treatment-by-region interaction.

Renal biopsy class

Table 30. PERR at Week 104 By Baseline Renal Biopsy Class (IPD/TF/WD=NR) (Double-Blind, mITT Population)

Baseline Renal Biopsy Class Subgroup	Placebo N=223	BEL N=223
Class III or IV, n	132	126
Responders, n (%)	42 (31.8)	60 (47.6)
SE %Responders	4.05	4.45
Observed difference vs. placebo	-	15.8
Odds ratio (95% CI) vs. placebo	-	1.82 (1.08, 3.08)
p-value	-	0.0250
Class III + V or Class IV + V, n	55	61
Responders, n (%)	15 (27.3)	23 (37.7)
SE %Responders	6.01	6.21
Observed difference vs. placebo	-	10.4
Odds ratio (95% CI) vs. placebo	-	1.76 (0.77, 4.05)
p-value	-	0.1796
Class V, n	36	36
Responders, n (%)	15 (41.7)	13 (36.1)
SE %Responders	8.22	8.01
Observed difference vs. placebo	-	-5.6
Odds ratio (95% CI) vs. placebo	-	0.65 (0.23, 1.86)
p-value	-	0.4196
Interaction Test p-value	-	0.2784

Statistics notes: Odds Ratio (OR), the OR 95% confidence interval (CI), and p-value are from a logistic regression model for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR. Interaction p-value is from a logistic regression model for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, baseline eGFR, baseline renal biopsy subgroup (Class III or Class IV, Class III+V or Class IV+V, Class V), and treatment-by-baseline-renal-biopsy-category interaction.

Secondary endpoint, CRR

Similar to the subgroup analyses of the PERR at Week 104, Odd Ratios for the CRR at Week 104 subgroup analyses numerically favoured the belimumab group for all subgroups with the exception of the Americas excluding US/Canada region subgroup and the baseline renal biopsy Class V subgroup.

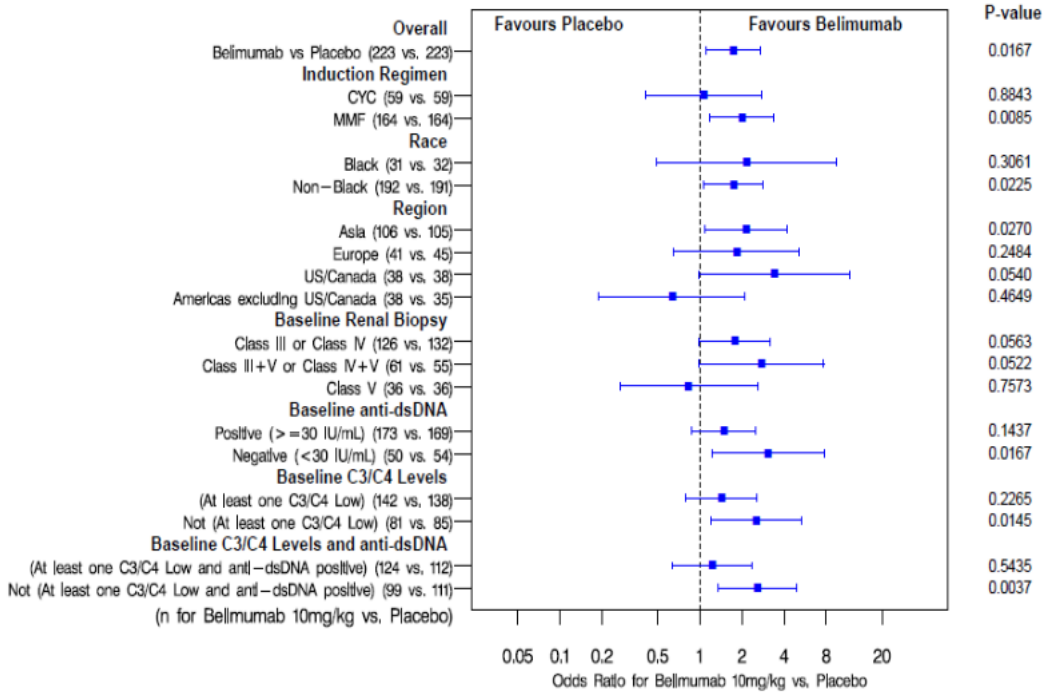


Figure 21. Odds Ratio of Complete Renal Response at Week104 by Subgroups (IPD/TF/WD=NR) (Double-blind, mITT Population)

Selected subgroups are presented in more detail below.

Region

Table 31. CRR at Week 104 By Region (IPD/TF/WD=NR) (Double-Blind, mITT Population)

Region Subgroup	Placebo N=223 n (%)	BEL N=223 n (%)
Asia, n	105	106
Responders, n (%)	21 (20.0)	36 (34.0)
SE %Responders	3.90	4.60
Observed difference vs. placebo		13.96
Odds ratio (95% CI) vs. placebo		2.15 (1.09, 4.23)
p-value		0.0270
Europe, n	45	41
Responders, n (%)	9 (20.0)	12 (29.3)
SE %Responders	5.96	7.11
Observed difference vs. placebo		9.27
Odds ratio (95% CI) vs. placebo		1.84 (0.65, 5.18)
p-value		0.2484
US/Canada, n	38	38
Responders, n (%)	5 (13.2)	11 (28.9)
SE %Responders	5.48	7.36
Observed difference vs. placebo		15.79
Odds ratio (95% CI) vs. placebo		3.41 (0.98, 11.86)
p-value		0.0540
Americas excluding US/Canada, n	35	38
Responders, n (%)	9 (25.7)	8 (21.1)
SE %Responders	7.39	6.61
Observed difference vs. placebo		-4.66
Odds ratio (95% CI) vs. placebo		0.64 (0.19, 2.12)
p-value		0.4649
Interaction Test p-value		0.3433

Statistics notes: Odds Ratio (OR), 95% confidence interval (CI), and p-value are from a logistic regression model run within the subgroup level for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR. Interaction p-value is from a logistic regression model for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, baseline eGFR, region (Asia, Europe, US/Canada, Americas excluding US/Canada), and treatment-by-region interaction.

Renal biopsy class

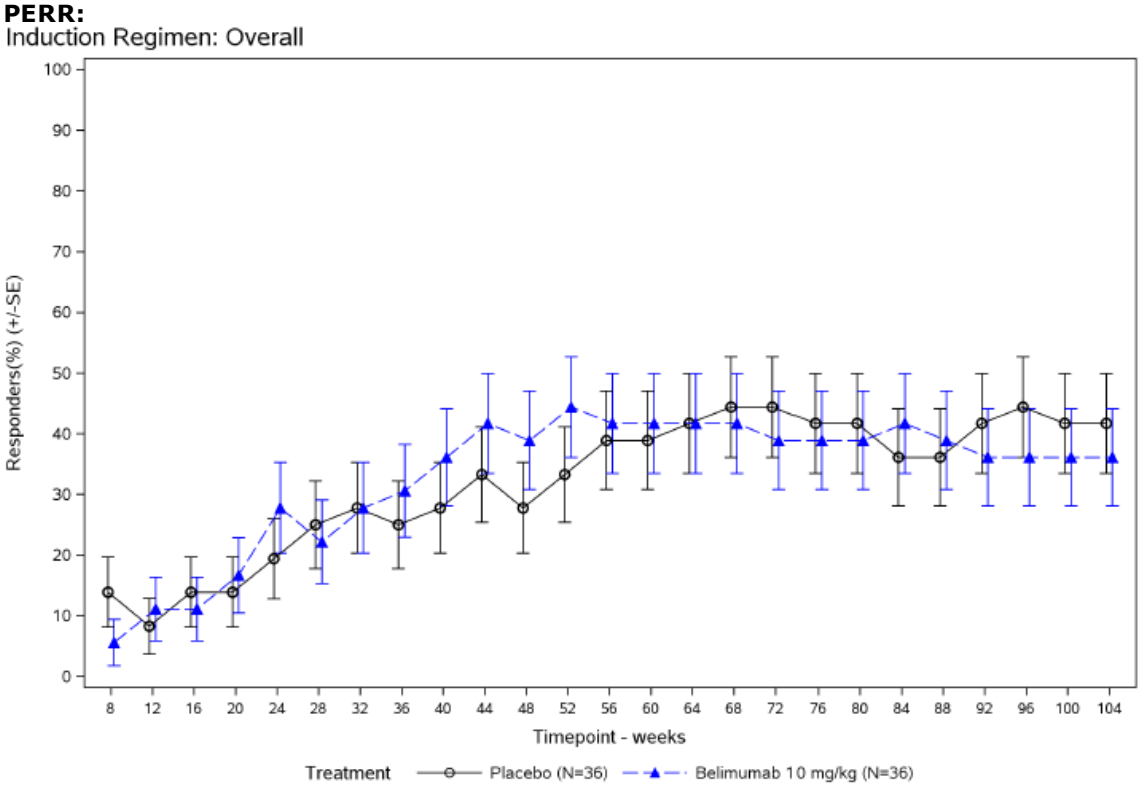
Table 32. CRR at Week 104 By Baseline Renal Biopsy Class (IPD/TF/WD=NR) (Double-Blind, mITT Population)

Baseline Renal Biopsy Class Subgroup	Placebo N=223	BEL N=223
Class III or IV, n	132	126
Responders, n (%)	25 (18.9)	39 (31.0)
SE %Responders	3.41	4.12
Observed difference vs. placebo	-	12.0
Odds ratio (95% CI) vs. placebo	-	1.78 (0.98, 3.21)
p-value	-	0.0563
Class III + V or Class IV + V, n	55	61
Responders, n (%)	8 (14.5)	16 (26.2)
SE %Responders	4.75	5.63
Observed difference vs. placebo	-	11.7
Odds ratio (95% CI) vs. placebo	-	2.76 (0.99, 7.72)
p-value	-	0.0522
Class V, n	36	36
Responders, n (%)	11 (30.6)	12 (33.3)
SE %Responders	7.68	7.86
Observed difference vs. placebo	-	2.8
Odds ratio (95% CI) vs. placebo	-	0.83 (0.27, 2.62))
p-value	-	0.7573
Interaction Test p-value	-	0.4300

Statistics notes: Odds Ratio (OR), 95% confidence interval (CI), and p-value are from a logistic regression model run within the subgroup level for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR. Interaction p-value is from a logistic regression model for the comparison between Belimumab and Placebo with covariates treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, baseline eGFR, baseline renal biopsy subgroup (Class III or Class IV, Class III+V or Class IV+V, Class V), and treatment--by-baseline-renal-biopsy-category interaction.

Efficacy results in the Class V subgroup were explored further. While no differences between treatment groups were observed for the percentage of PERR and CRR responders at Week 104, there was a higher percentage of PERR and CRR responders in the belimumab group compared to placebo at earlier visits (Figure 22). According to the applicant, evidence of earlier proteinuria reduction in belimumab treated subjects with Class V LN, and the numerically greater response with belimumab observed in the Class III+V/IV+V subgroup, which would require improvement of Class V nephritis, may suggest potential efficacy of belimumab in Class V LN.

PERR:



CRR:

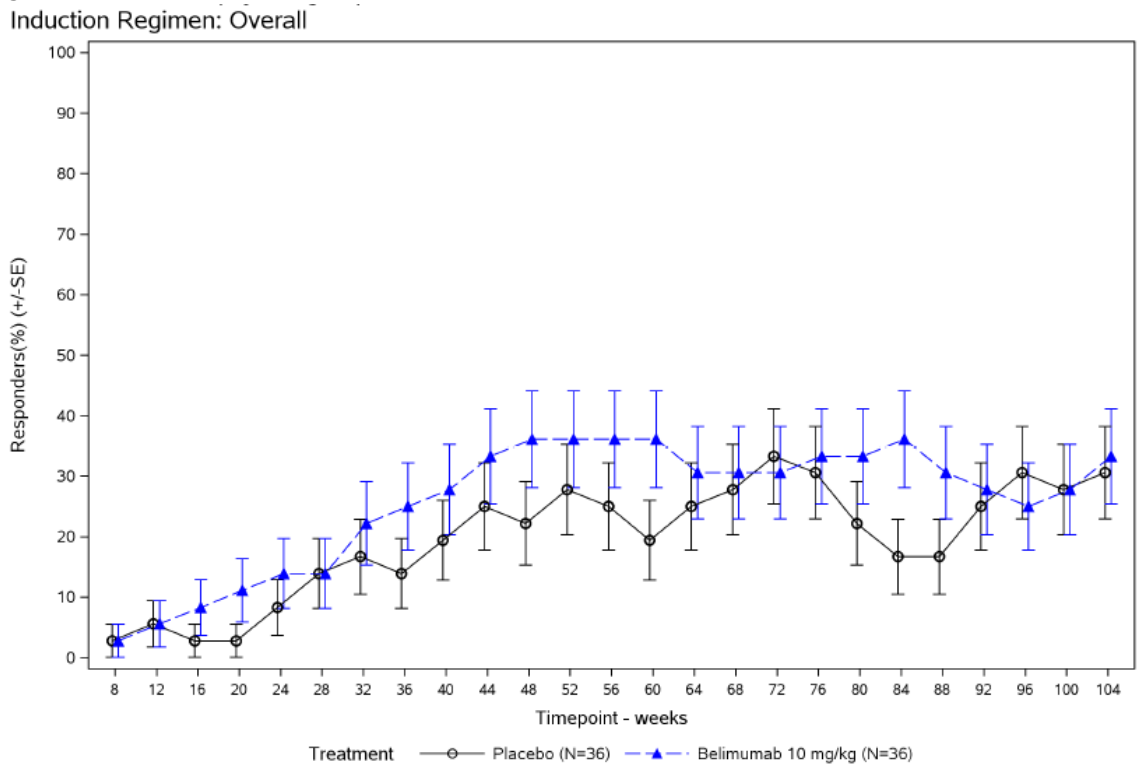


Figure 22. Class V Renal Biopsy Subgroup, PERR and CRR by Visit (Double-blind; mITT Population)

Efficacy by Baseline Proteinuria Subgroups

In addition to the pre-specified subgroups, a *post hoc* analysis of key efficacy outcomes by baseline proteinuria subgroups was completed to further explore the impact on efficacy.

Table 33. Disposition of PERR and CRR by Baseline Proteinuria Subgroups

Subgroup	Baseline uPCR <3 g/g		Baseline uPCR >=3 g/g	
	Placebo N=131	BEL N=132	Placebo N=92	BEL N=91
PERR				
Responders, n (%)	44 (33.6)	72 (54.5)	28 (30.4)	24 (26.4)
Non-responder, n (%)	87 (66.4)	60 (45.5)	64 (69.6)	67 (73.6)
IP ± study discontinuation without prior TF, n (%)	28 (21.4)	22 (16.7)	15 (16.3)	27 (29.7)
Insufficient renal response due to uPCR and/or eGRF and/or TF, n (%)	59 (45.0)	38 (28.8)	49 (53.3)	40 (43.9)
CRR				
Responders, n (%)	29 (22.1)	51 (38.6)	15 (16.3)	16 (17.6)
Non-responder, n (%)	102 (77.9)	81 (61.4)	77 (83.7)	75 (82.4)
IP ± study discontinuation without prior TF, n (%)	28 (21.4)	22 (16.7)	15 (16.3)	27 (29.7)
Insufficient renal response due to uPCR and/or eGRF and/or TF, n (%)	74 (56.5)	59 (44.7)	62 (67.4)	48 (52.7)

Other renal outcomes

Change in proteinuria over time

The median *percent* (Figure 23) and *absolute* (Figure 24) change from baseline in uPCR decreased over time for both the placebo and belimumab group.

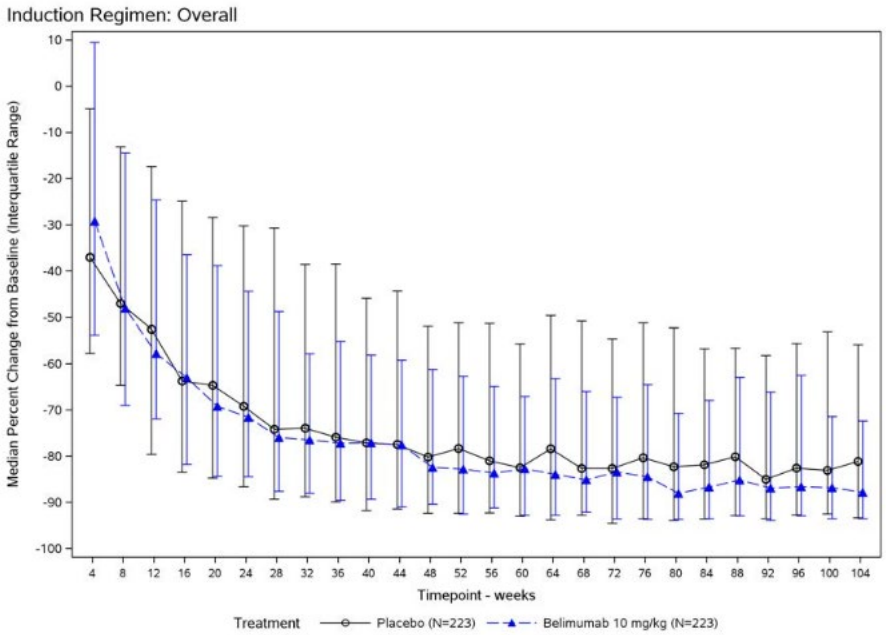


Figure 23. uPCR Percent Change from Baseline by Visit While on Treatment (Observed)

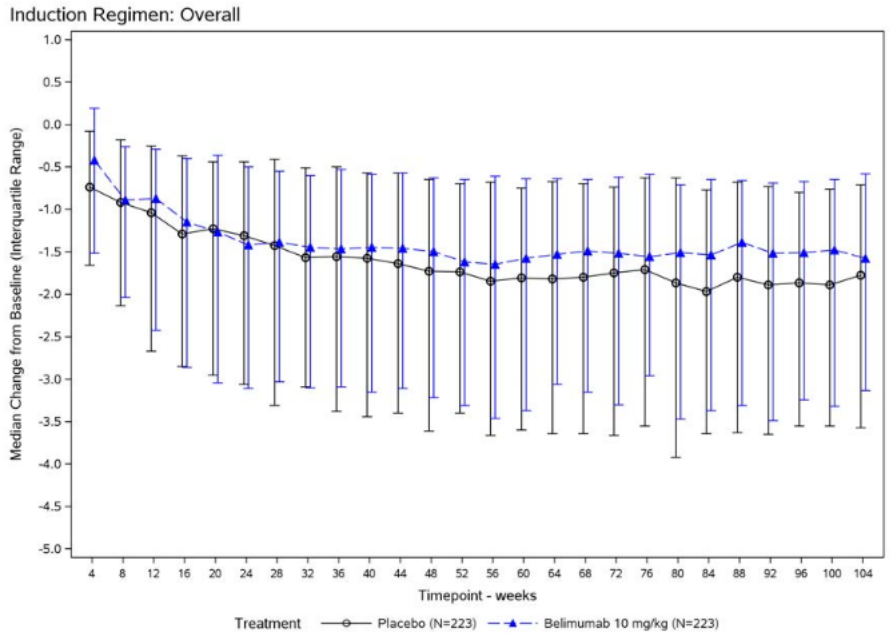


Figure 24. uPCR Change from Baseline by Visit While on Treatment (Observed)

Absolute eGFR Values Over Time

Figure 25 presents mean observed GFR values (from creatinine adjusted for BSA; mL/min/1.73m2) by visit.

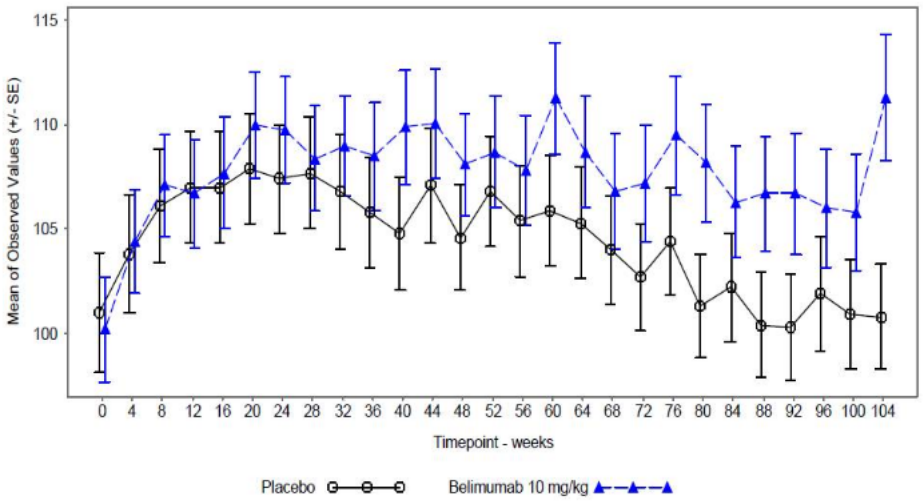


Figure 25. Mean Observed GFR (from Creatinine Adjusted for BSA; mL/min/1.73m^2) Values by Visit (Double-Blind; Safety Population)

Other endpoints of interest

Corticosteroid use

Corticosteroid use was converted to a prednisone-equivalent dose and, thus, is referred to as average daily prednisone dose. Figure 26 graphically presents by visit the proportion of subjects receiving an average daily prednisone dose ≤5 mg since the previous visit through Week 104, regardless of whether or not response was achieved.

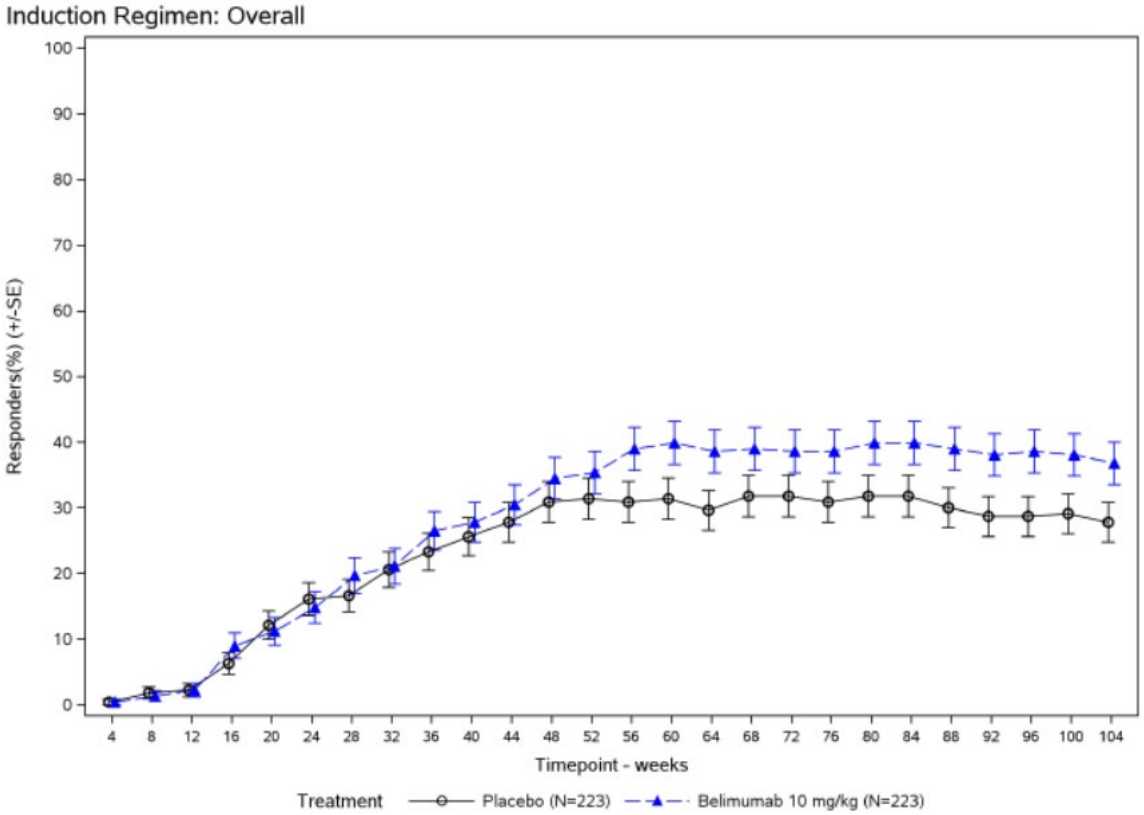


Figure 26. Prednisone ≤5 mg Average Daily Dose Since Previous Visit (IPD/TF/WD=NR) (Double-Blind, mITT Population)

The proportion of subjects in the overall mITT population who received an average daily prednisone dose of ≤7.5 mg since the previous visit is shown below.

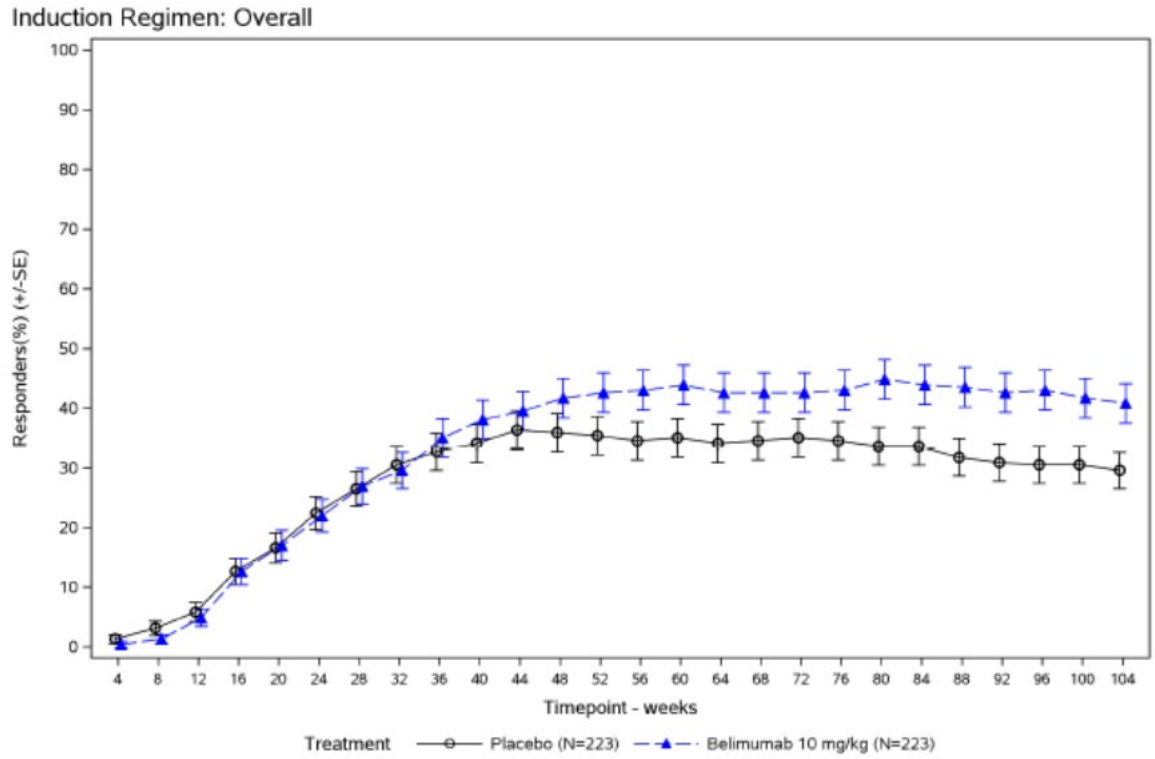


Figure 27. Prednisone ≤7.5 mg Average Daily Dose Since Previous Visit (IPD/TF/WD=NR) (Double-blind, mITT)

Summary of main study

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 34 ***Summary of Efficacy for trial BEL114054***

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Belimumab plus Standard of Care versus Placebo plus Standard of Care in Adult Subjects with Active Lupus Nephritis			
Study identifier	BEL114054		
Design	Randomized, Double-Blind, Placebo-Controlled Study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		104 weeks Not applicable 28 weeks
Hypothesis	Superiority		
Treatments groups	Placebo		N=223
	Belimumab		N=223
Endpoints and definitions	Primary endpoint	PERR w 104	Primary Efficacy Renal Response at Week 104
	Major secondary endpoint	CRR w 104	Complete Renal Response at Week 104
	Major secondary endpoint	PERR W 52	Primary Efficacy Renal Response at Week 52
	Major secondary endpoint	Time to Renal-Related Event or Death	Defined as first of the following: i) Death ii) end stage renal disease (ESRD), iii) doubling of serum creatinine, iv) renal worsening bas evidenced by increased proteinuria and/or impaired renal function, or v) renal disease-related treatment failure
Database lock	25-Jul-2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Placebo	Belimumab
	Number of subject	223	223
	Primary endpoint		
	PERR W 104	72 (32.3%)	96 (43.0%)
	Major secondary endpoints		
	CRR W 104	44 (19.7%)	67 (30.0%)
	PERR W 52	79 (35.4%)	104 (46.6%)
	Time to renal-related event or death	63 (28.3%)	35 (15.7%)
	Primary endpoint		

Effect estimate per comparison	Primary endpoint (PERR W 104)	Comparison groups	Belimumab vs placebo
		Difference (%)	10.76
		OR (95% CI)	OR=1.55 (1.04, 2.32)
		P value	0.0311
	Major secondary endpoints		
	CRR W 104	Comparison groups	Belimumab vs placebo
		Difference (%)	10.31
		OR (95% CI)	OR=1.74 (1.11, 2.74)
		P value	0.0167
	PERR W 52	Comparison groups	Belimumab vs placebo
		Difference (%)	11.21
		OR (95% CI)	OR=1.59 (1.06, 2.38)
		P value	0.0245
	Time to renal-related event or death	Comparison groups	Belimumab vs placebo
		Difference (%)	-
		HR (95% CI)	HR=0.51(0.34, 0.77)
		P value	0.0014

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The approval of belimumab (Benlysta) for treatment of SLE was based on clinical trials in subjects with active SLE receiving standard therapy. Subjects with severe active renal lupus were excluded from these trials. The indication initially sought by the MAH was as follows: *treatment of lupus nephritis in adult patients who are receiving standard therapy*.

BEL114054 was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, 104-week study to evaluate the efficacy and safety of IV belimumab 10 mg/kg plus standard of care compared to placebo plus standard of care in adult subjects with active LN (histological classes III, IV, V or V in combination with III or IV LN). Eligible subjects were 18 years or older in age with active, biopsy- proven proliferative lupus nephritis Class III or IV [excluding Class III(C), IV-S(C), and IV-G(C)], either with or without the presence of Class V, or pure Class V membranous disease using the 2003 ISN/RPS criteria. All patients had SLE according to the ACR and SLICC (biopsy-proven LN in combination with ANA or anti-dsDNA) classification criteria. This is in line with EMA Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2013 corr 1, referred to as "EMA Guideline" hereafter) and acceptable to the CHMP. Active disease was defined as urinary protein:creatinine ratio of ≥1.0 and either active urinary sediment, confirmatory biopsy within 3 months or proteinuria ≥3.5 grams/day.

Patients were randomised to either 10 mg/kg belimumab or placebo for 104 weeks, both on top on standard of care with high dose corticosteroids and either:

-Cyclophosphamide according to the Euro-Lupus regimen (500 mg by IV infusion every 2 weeks for 6 infusions), followed by azathioprine with a target dose of 2 mg/kg/day

- Mycophenolate mofetil (MMF) 0.5 g twice a day (bid) for the first week, increase to 1 g bid for the second week, and then 1.5 g bid for the third and subsequent weeks.
Mycophenolate sodium could be used in lieu of MMF for induction and/or maintenance therapy (recommended dose from 720 mg/day to 2160 mg/day).

The dosing regimen is in line with the 2019 EULAR recommendations for the management of systemic lupus erythematosus.

The randomization was stratified by their induction/maintenance regimen (HDCS plus CYC followed by AZA vs HDCS plus MMF followed by MMF) and race (black race vs other). According to the EMA Guideline, "*Patients should be stratified at randomisation by relevant baseline characteristics e.g. histological class of lupus nephritis, level of proteinuria, and/or creatinine clearance"*. Furthermore, "*care should therefore be taken that both study arms include comparable numbers of patients of different ethnic background".* Although it would have been valuable to stratify also for the factors exemplified in the EMA Guideline, the currently used stratification factors are considered relevant and acceptable to the CHMP.

The primary efficacy endpoint was the PERR at Week 104 measured as a dichotomous response (Responder vs. Non-Responder). A responder is defined as uPCR ≤0.7 and eGFR is no more than 20% below pre-flare value or ≥60 mL/min/1.73m^2 and-Not a Treatment Failure. The 4 major secondary efficacy endpoints were: CRR at Week 104, PERR at Week 52, Time to Death or Renal-related Event, and ORR at Week 104. According to the EMA Guideline, "*Studies conducted in patients with lupus nephritis should be aimed for the control of renal activity*. *It is expected that primary endpoints should be contextualised by reference to clinically meaningful values for major/complete response, such as normalisation/return to baseline of measured GFR or proteinuria of <0.5 g/24-h. A partial response, i.e. not full recovery but renal response able to maintain an eGFR within pre-specified margins with respect to baseline values, could only be accepted as primary endpoint if prospectively defined and relevance is well justified*". Thus, the EMA recommended primary endpoint of **complete renal response** differs from the primary efficacy renal response used in this study which is a **partial response**. Therefore, CHMP assessment was much focused on the secondary endpoint of CRR.

The EMA Guideline also recommends to assess prevention of long-term damage. Although this is highly clinically relevant, the study duration is too short to allow safe conclusions on such an outcome. However, this issue was not further pursued by the CHMP since prevention of long-term damage is partly covered by the CRR which has been associated with favourable long-term renal prognosis in the context of RCTs and long-term observational studies (Kostopoulou, Curr Rheum Rep 2020 22:30[27])..

There were many important protocol amendments throughout the study, including several changes to the primary endpoint:

- The first subject was included in the study on **12 Jul 2012**, and the last visit in the double-blind phase occurred on 25 July 2019.
- In Protocol Amendment 6 (dated **25 Apr 2017**) the primary endpoint of ORR was updated to remove the urinary sediment component and use estimated GFR for evaluation of kidney function. According to the MAH, this change to modified ORR was driven by the latest medical practice suggesting that urinary sediment level was not an appropriate measure for disease change in lupus nephritis as reported in the recent publications on the long-term predictors of renal outcomes in patients with LN and the sponsor's experience in urinalysis data collection in a multicenter trial setting. Calculated GFR based on 24-hour urine collections used in the CRR definition was changed to estimated GFR to minimize bias due to sample collection errors. From a clinical point of view, the rationale for these changes is agreed by the CHMP.

  Concurrently, the primary analysis method was updated from a Van Elteren test to a rank analysis of covariance (ANCOVA). Use of a Rank ANCOVA allowed the analysis to adjust for the continuous covariates of baseline uPCR, and baseline eGFR as well as the stratification factors of induction regimen (CYC vs MMF), and race (Black vs Non- black). The inclusion of additional baseline covariates had the potential to increase power. The change of analysis method is agreed by CHMP since it allows the use of covariates in line with the EMA guideline on *Adjustment for*

[27]Kostopoulou, Myrto, Christina Adamichou, and George Bertsias. "An Update on the Diagnosis and Management of Lupus Nephritis." Current Rheumatology Reports 22 (2020): 1-12.

baseline covariates in clinical trials (EMA/CHMP/295050/2013) and was performed before unblinding of any data.

The original study primary endpoint of ORR including urinary sediment and calculated GFR at Week 104 (IPD/TF/WD=NR; Van Elteren test) was included as a pre-planned sensitivity analysis. The results favoured belimumab but **were not statistically significant**. Thus, this change impacted the outcome of the study, in favour of the sponsor.

- In Protocol Amendment 7 (dated **24 Jan 2019**) the primary endpoint was updated from the modified ORR to the PERR. The ORR had 3 levels (complete, partial or no response) however the PERR had 2 levels (response, or no response) similar to the major secondary endpoint of CRR which was analyzed by logistic regression. Therefore, the analysis method selected for the PERR was also a logistic regression. The previous primary endpoint of modified ORR analyzed using a Rank ANCOVA was retained as a key secondary endpoint in the prespecified hierarchy. Modified ORR demonstrated statistical significance in favour of the belimumab group compared with placebo (p=0.0096). Although the rationale behind this change is not completely understood, CHMP concluded that this change did not affect the results in favour of the sponsor.

The CHMP raised concerns about the impact of the changes to the primary endpoint on the reliability of the study results. Upon CHMP' request, the MAH clarified that these changes were made prior to unblinding of the study results on **08 Nov 2019**. Furthermore, the MAH clarified that the sponsor, study site personnel and the CROs were blinded to the investigational product received and to the results of certain biomarker and pharmacodynamic laboratory results with potential for unblinding (such as B cell subsets). This is particularly reassuring, since the B cell depleting mode of action of Benlysta might easily help to identify patients treated with active drug through laboratory monitoring.

It was also noted that the clinically most important endpoint of CRR recommended in the EMA Guideline was affected by these protocol amendments, since the urinary sediment component was removed. According to the EMA Guideline, induction of major/complete renal response should be "*demonstrated as clinically significant improvement of renal function during induction phase e.g. by improvement of eGFR and reducing renal injury, primarily protein excretion and findings in active urinary sediment*". Nonetheless, from a clinical point of view, the removal of the urinary sediment item is considered acceptable to the CHMP.

The CHMP was also concerned about the timing for change to the primary endpoint since the first change occurred in 2017 i.e. 5 years after the first patient entered the study. However, the MAH clarified that the revisions to the study protocol were agreed with EMA before implementation to the study (change from ORR to mORR: variation II/0049, change from mORR to PERR: variation II/0062) and that no laboratory parameters were unblinded prior to unblinding of the study. Therefore, the CHMP concluded that the changes to the primary endpoint were not data driven.

Overall, the CHMP concluded that the changes to the primary endpoint are clinically and statistically motivated and that they were made without knowledge of the outcome of the study.

Important protocol deviations were frequent and occurred in more than 50% of the patients. The largest proportion of important protocol deviations was in the category of assessments and/or procedures. The MAH clarified that important protocol deviations that could affect key efficacy evaluations and lead to subject's exclusion from PP population were prespecified in the Reporting and Analysis Plan (RAP) based on the ICH/E6, E3, E9 guidelines. The PP set would only be analysed if this population excluded more than 15% of the mITT population. Since only 11 (2.5%) patients were excluded from the PP population due to important protocol deviations that could affect key efficacy analyses, no PP analysis was performed. This was agreed by the CHMP.

Efficacy data and additional analyses

A total of 448 patients were included in the study (n=224 in each arm). All randomised patients were included in the safety population. More subjects in the placebo arm discontinued from the study (40.8% for placebo vs 34.5% for belimumab). The main reason for discontinuation in both arms was adverse event. A total of two patients were excluded from the mITT population because of GCP issues. This is acceptable to CHMP. Most patients were female (almost 90%), and of Asian origin (50%). Only 33% were Caucasian. This can be expected because of the higher prevalence in Asian and black populations, however differences in treatment response can differ between populations and subgroup analyses are important, as further discussed hereafter.

A total of 88% of the patients had a class III or IV nephritis, with or without elements of class V. Pure membranous (class V) nephritis was found in 16.1% of the patients. Significant proteinuria (>0.5 g/g) was found in 95% of the patients. There were no important differences between the treatment groups. All patients fulfilled the ACR nephritis criterion. There were no important differences between the groups with regards to ACR criteria. MMF was the most frequently used induction therapy (73.5% in both arms). The mean prednisone dose was 69.5 mg. Concomitant antimalarials was used by 71.7% of the patients (slightly higher in the belimumab group), and immunosuppressants by 87.4%. ACEi or ARB were used with a similar frequency in both groups (~65%).

The primary endpoint, PERR at week 104, was achieved by 72/223 patients (32.3%) in the placebo group and 96/223 patients (43%) in the belimumab group. The more important secondary endpoint CRR at the same timepoint was achieved by 44/223 patients (19.7%) in the placebo group and 67/223 patients (30%) in the belimumab group. The difference is statistically significant and clinically relevant. Treatment group, induction regimen (CYC vs. MMF), race (Black vs. Non-Black), baseline uPCR, and baseline eGFR were included as covariates in the analyses. The results of the components of the PERR and CRR were all in favour of belimumab. The risk for renal-related event or death was lower in the belimumab arm.

For the predefined subgroup of European patients, there was no convincing difference between the groups for PERR, while the difference on CRR was more convincing (9/45 patients, 20% for placebo and 12/41 patients, 29.3% for belimumab). Furthermore, an inferior effect in patients from America excluding US/Canada was observed. This was found particularly important based on the knowledge that patients with proliferative nephritis of African/Hispanic origin have a worse prognosis than other patients.

The MAH was therefore asked by the CHMP to discuss differences in treatment effect in patients of different ethnicity (not regions). In response, the MAH presented data on the Hispanic population, overall and separate for US/Canada and America excluding US/Canada. The inferior efficacy for belimumab than compared to placebo seemed to be restricted to America excluding US/Canada only. When looking at non-Hispanics in the same region, the same pattern was observed. The inferior efficacy for belimumab seemed to be observed in the America-non-US/Canada region, regardless of ethnicity. The MAH has also presented post-hoc analyses of efficacy across race (Asian, White, Black, American Indian or Alaskan Native), where the results for the primary and secondary endpoint displays the same pattern as in the overall analyses. The MAH concluded that the results in the overall Hispanic population were driven by the negative treatment effect observed in the Americas excluding US/Canada, while in the US/Canada region both Hispanics and non-Hispanics benefited from belimumab treatment, and that the efficacy results in the Americas excluding US/Canada region were not driven by any particular race or ethnicity. The CHMP agrees with the MAH's conclusion that there is no clear explanation to these findings and that there is no evidence that efficacy of Benlysta is influenced by any particular race or ethnicity.

Subgroup analyses showed that the efficacy is most prominent in the subgroup of patients treated with concomitant MMF, and the difference for Benlysta vs placebo is smaller in the subgroup of patients treated with concomitant cyclophosphamide.

In the pre-specified subgroup analysis of renal biopsy class, there seemed to be no increased efficacy measured as PERR for belimumab than compared to placebo for patients with a pure membranous nephritis (class V). Class V nephritis is a distinct clinical entity characterised by proteinuria, often within nephrotic-range (>3.5 g/day).

In patients with high baseline proteinuria (>=3g/g), there were no (PERR) or very small (CRR) increase in treatment response for the belimumab group compared to the placebo group. The uPCR percent change from baseline was similar for the belimumab and placebo groups at week 104. This was of concern to the CHMP, since these are the patients with the worst prognosis. The MAH argued that patients with high proteinuria have more advanced LN with lower response rates due to longer time to proteinuria recovery and lower likelihood of complete response. Furthermore, hypocomplementemia, higher SLE activity, and low renal function were reported to be associated with more refractory renal disease and poorer ability to respond to treatment. Review of demographics and baseline characteristics by baseline proteinuria status using the 3 g/g threshold revealed that subjects in the ≥3 g/g proteinuria subgroup had higher SLEDAI-S2K scores, lower eGFR and higher rates of organ damage compared to the <3 g/g subgroup.

However, patients with high proteinuria are at high unmet need for new treatments. Standard treatment also for these patients is CYC or MMF, with MMF being first line treatment in class V LN with nephrotic proteinuria. According to EULAR guidelines, in refractory or relapsing disease, off-label treatment with RTX may be considered. There is some support for MMF and high-dose CYC in severe forms of LN associated with increased risk of progression into end-stage renal disease (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis). Furthermore, calcineurin inhibitors may be considered as second-line agents for induction or maintenance therapy mainly in membranous LN, podocytopathy, or in proliferative disease with refractory nephrotic syndrome, despite standard-of-care within 3–6 months. Thus, there are no approved treatments for these patients that treatment. Therefore, the CHMP agreed that the use of belimumab in this group could be supported by the efficacy primarily based on the small observed increase in CRR compared to placebo even though limited. Nonetheless, the MAH was requested to further justify the efficacy for this subgroup of patients with nephrotic range proteinuria, with special focus on reduction of proteinuria. In their response, the MAH presented a reasonable rationale as to why patients with nephrotic-range proteinuria were less likely to respond to therapy, referring to publications describing association with longer time to proteinuria resolution and lower likelihood of complete response in these patients. In some studies, more than 5 years was needed to achieve complete renal response. The MAH argued that although belimumab did not increase the renal response or remission rate compared to treatment with only cyclophosphamide or MMF, there seemed to be a benefit when it comes to renal-related event or death also in patients with high baseline proteinuria. The MAH's argumentation was acceptable to the CHMP, and the issue on the post-hoc efficacy analysis across subgroups of baseline proteinuria was not further pursued.

The lower belimumab exposure in subjects with high baseline proteinuria and its impact on the efficacy results is discussed in the PK assessment (Section 2.3.5. of the assessment report). The available data do not support a dose adjustment in subjects with high baseline proteinuria.

In the overall population, a small numerical difference in percental reduction of proteinuria is shown in favour of belimumab, however the absolute reduction was numerically higher in the placebo group. This could possibly be explained by a slightly higher mean baseline proteinuria level at baseline for the placebo group. A gradual decline in mean eGFR values is observed for the placebo group starting from Week 52, while renal function seems relatively stable in belimumab treated subjects.

Corticosteroid use was not a multiplicity-controlled endpoint. A numerical higher proportion of patients in the belimumab arm was able to reduce steroids below 5 and 7.5 mg, respectively.

The initially proposed indication was not agreed by CHMP since it was too broad and included all biopsy classes of LN. Study BEL114054 did not include patients with class I or II nephritis whereas Benlysta is proposed for LN patients in combination with MMF or cyclophosphamide, which is not applicable for LN class I and II. The MAH argued that in the pivotal SLE studies, where patients with class I and II nephritis were eligible for inclusion i.e. Benlysta was given to patients with high disease activity despite standard therapy. However, the pivotal SLE studies were not designed to study the efficacy in the specific subgroup of class I and II LN patients. The MAH agreed upon the CHMP's request to revise the indication to patients with **active** lupus nephritis where treatment with background immunosuppressives is considered.

Since LN is a severe manifestation of SLE, the MAH was also requested to justify a separate LN indication from the SLE indication in patients with *active, autoantibody-positive SLE with a high degree of disease activity despite standard therapy* in order to apply the CHMP´s principles of wording of the indication (EMA/CHMP/483022/2019) foreseeing that if a study population is already covered by the already approved indication, an extension of the indication in section 4.1 of the SmPC is not accepted. The MAH clarified that in Study BEL114054 as in the claimed LN indication, treatment with Benlysta is first line therapy in combination with intensive immunosuppressants whereas the existing SLE indication is for use in patients who do not respond to standard treatment i.e., continue to have active disease "despite standard therapy". The CHMP agreed with the justification that the different place in therapy for Benlysta in SLE patients and the LN subgroup supports the inclusion of a separate LN indication.

Finally, the MAH was requested to justify the inclusion of Class V LN patient in the indication and to discuss the benefit of adding belimumab to SOC in this subgroup. The MAH presented data supportive of an efficacy in this subgroup, in particular a reduced risk for renal-related event or death. It is acknowledged by the CHMP that there is an overlap between class III/IV and class V nephritis, and that the subgroup of patients with pure class V nephritis was too small to enable firm conclusion. The CHMP agreed to a broad LN indication including patients with class V nephritis provided that the prescribers are clearly informed of the efficacy results on membranous LN (class V). Class V LN is a specific LN entity, and the efficacy in this subgroup is considered of importance for the prescribers. The MAH was thus requested to include the results in subgroups of patients with different biopsy classes in section 5.1 of the SmPC. The inclusion of these clinically relevant subgroup analyses in the SmPC is in line with the SmPC guideline, "*In the exceptional cases where clinically relevant information from subgroup or post-hoc analyses is presented; it should be identified as such in a balanced manner reflecting the limited robustness of both positive and negative secondary observations*". The MAH agreed to include a forest plot showing the primary endpoint for the prespecified subgroups in section 5.1 of the SmPC.

2.4.3. Conclusions on the clinical efficacy

The results from study BEL114054 show a statistically significant and clinically relevant effect for belimumab when it comes to primary and all major secondary endpoints.

The MAH agreed to revise the initially claimed broad indication upon the CHMP's request to following agreed indication (section 4.1 of the SmPC): *in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis (see sections 4.2 and 5.1).*

Subgroup analyses showed that the efficacy was most prominent in the subgroup of patients treated with background MMF, and in patients with histopathological class III/IV nephritis. Subgroup analyses results are included in Section 5.1 of the SmPC.

Furthermore, section 4.4 of the SmPC is updated to remove the statement that Benlysta has not been studied and is not recommended in severe active LN.

2.5. Clinical safety

Introduction

The safety profile of Benlysta includes infections, hypersensitivity and infusion/injection-related systemic reactions, and psychiatric events including depression and suicidality. Potential risks listed in the RMP include progressive multifocal leukoencephalopathy (PML), malignancies, immunogenicity, and effects on immunizations. At the approval of Benlysta, there was concern on an increased mortality for Benlysta than compared to placebo, primarily due to infections. A large PASS (BASE) including >4000 patients was recently finished. The results led to a DHPC on the risk for psychiatric events including depression and suicidality (II/65), and updates of the SmPC to include an increased risk for fatal infections (II/76).

Patient exposure

A total of 448 subjects were randomized in study BEL114054 (224 in each group), all of whom received at least 1 dose of IP and constitute the safety population.

The mean (SD) duration of exposure to study agent in the BEL114054 mITT population was 546.4 (251.3) days for placebo and 577.3 (243.5) days for belimumab. The median (range) duration of exposure was 726.0 (28 to 748) days in the placebo group and 727.0 (28 to 743) days in the belimumab group.

Adverse events

The AE presentations in this section are primarily for the on-treatment period. For subjects who did not continue into the OLE, the on-treatment period is defined by the treatment start date up to and including the treatment stop date +28 days or the date of IP discontinuation (whichever was longer). The AE must have started on or any time after the first dose of IP (having been absent pre-treatment or worsened relative to the pre-treatment state). AEs with missing start dates were assumed to be on-treatment. For those subjects who continued on to the OLE, the on-treatment stop date for the double-blind period was the date of the Week 104 infusion (as the Week 104 infusions represent Day 1 of the OLE) but any events pre-infusion on that day are part of the double-blind period. AEs reported on the day of the first OLE-infusion are accounted for in both study periods.

Additionally, pre- and post-treatment AE summaries were generated. The pre-treatment period is defined as the date prior to the first dose of IP. The start of post-treatment period is defined by the start date of the first missed dose of IP +1 day or 29 days after the last dose of IP (whichever was longer). For all subjects, AEs were to be reported through 8 weeks after the last IP administration. For subjects who discontinued IP but remained in the study, SAEs collection continued through Week 104.

It was expected that there would be different safety profiles observed during the first 24 weeks of treatment (induction phase) and post Week 24 (maintenance phase) due to high disease activity with high levels of proteinuria and intensive immunosuppressive therapy during the induction phase. Therefore, summaries were generated for AEs during first 24 weeks which included induction therapy and for AEs during the maintenance phase (post Week 24). Differences in AEs between the time periods (where relevant) are discussed.

Adverse event summary

An overall summary of incidence of AEs for the on-treatment period is provided in Table 35.

Table 35. Adverse Events Summary (Double-Blind, Safety Population)

	CYC/AZA		MMF		Overall	
At least one:	Placebo N=59 n (%)	Belimumab 10 mg/kg N=60 n (%)	Placebo N=165 n (%)	Belimumab 10 mg/kg N=164 n (%)	Placebo N=224 n (%)	Belimumab 10 mg/kg N=224 n (%)
AE	54 (91.5)	56 (93.3)	157 (95.2)	158 (96.3)	211 (94.2)	214 (95.5)
Related AE	31 (52.5)	35 (58.3)	88 (53.3)	88 (53.7)	119 (53.1)	123 (54.9)
Serious AE	14 (23.7)	18 (30.0)	53 (32.1)	40 (24.4)	67 (29.9)	58 (25.9)
IP-Related Serious AE	3 (5.1)	9 (15)	22 (13.3)	14 (8.5)	25 (11.2)	23 (10.3)
Severe AE	13 (22.0)	16 (26.7)	35 (21.2)	38 (23.2)	48 (21.4)	54 (24.1)
AE resulting in IP discontinuation	5 (8.5)	8 (13.3)	24 (14.5)	21 (12.8)	29 (12.9)	29 (12.9)
AE resulting in study withdrawal	1 (1.7)	1 (1.7)	7 (4.2)	4 (2.4)	8 (3.6)	5 (2.2)
AE resulting in IP discontinuation and/or withdrawal from study	5 (8.5)	8 (13.3)	24 (14.5)	21 (12.8)	29 (12.9)	29 (12.9)
All Deaths[a]	0	1 (1.7)	5 (3.0)	5 (3.0)	5 (2.2)	6 (2.7)
On-Treatment Fatal SAE[b]	0	1 (1.7)	3 (1.8)	3 (1.8)	3 (1.3)	4 (1.8)
Post-Treatment Fatal SAE[c]	0	0	2 (1.2)	2 (1.2)	2 (0.9)	2 (0.9)

Source: Table 3.02, Table 3.24 (for IP-related SAE row), Listing 3.05 and Table 3.75 (for all deaths).
Notes: Only on-treatment data is displayed (except for All Deaths and Post-Treatment Fatal SAE), see RAP Section 14.6.1.6 for definition.
Subjects are counted once in each row and column for which they have any AE meeting the criterion; percentages are of the N for the column.
a. Includes all deaths that occurred during the double-blind phase including off-treatment.
b. Developed fatal SAEs while on study treatment while death may have occurred anytime thereafter.
c. Fatal SAEs occurred after the on-treatment period.
AE = Adverse event.
IP = Investigational product.
SAE = Serious adverse event.

Adverse Events by System Organ Class

The system organ classes (SOCs) with >30% of subjects (in both groups) experiencing an AE were infections and infestations (76.3% placebo, 82.1% belimumab), gastrointestinal (GI) disorders (47.3% placebo, 45.1% belimumab), musculoskeletal and connective tissue disorders (36.2% placebo, 32.6% belimumab) and skin and subcutaneous tissue disorders (31.3% placebo, 33.9% belimumab) (Table 36).

The 3 SOCs with a >5% difference between treatment groups overall were infections and infestations (76.3% placebo, 82.1% belimumab), general disorders and administration site conditions (28.1% placebo, 22.8% belimumab) and respiratory, thoracic and mediastinal disorders (21.4% placebo, 27.7% belimumab).

Table 36. Adverse Events by System Organ Class (Double-Blind, Safety Population)

	CYC/AZA		MMF		Overall	
System Organ Class[a]	Placebo N=59 n (%)	Belimumab 10 mg/kg N=60 n (%)	Placebo N=165 n (%)	Belimumab 10 mg/kg N=164 n (%)	Placebo N=224 n (%)	Belimumab 10 mg/kg N=224 n (%)
Infections and infestations	40 (67.8)	45 (75.0)	131 (79.4)	139 (84.8)	171 (76.3)	184 (82.1)
Gastrointestinal disorders	24 (40.7)	28 (46.7)	82 (49.7)	73 (44.5)	106 (47.3)	101 (45.1)
Musculoskeletal and connective tissue disorders	24 (40.7)	26 (43.3)	57 (34.5)	47 (28.7)	81 (36.2)	73 (32.6)
Skin and subcutaneous tissue disorders	22 (37.3)	28 (46.7)	48 (29.1)	48 (29.3)	70 (31.3)	76 (33.9)
Nervous system disorders	19 (32.2)	18 (30.0)	42 (25.5)	38 (23.2)	61 (27.2)	56 (25.0)
General disorders and administration site conditions	19 (32.2)	21 (35.0)	44 (26.7)	30 (18.3)	63 (28.1)	51 (22.8)
Respiratory, thoracic and mediastinal disorders	9 (15.3)	22 (36.7)	39 (23.6)	40 (24.4)	48 (21.4)	62 (27.7)
Blood and lymphatic system disorders	16 (27.1)	16 (26.7)	33 (20.0)	27 (16.5)	49 (21.9)	43 (19.2)
Investigations	13 (22.0)	17 (28.3)	34 (20.6)	24 (14.6)	47 (21.0)	41 (18.3)
Metabolism and nutrition disorders	12 (20.3)	9 (15.0)	32 (19.4)	35 (21.3)	44 (19.6)	44 (19.6)
Injury, poisoning and procedural complications	7 (11.9)	9 (15.0)	17 (10.3)	25 (15.2)	24 (10.7)	34 (15.2)
Vascular disorders	9 (15.3)	9 (15.0)	22 (13.3)	14 (8.5)	31 (13.8)	23 (10.3)
Reproductive system and breast disorders	9 (15.3)	7 (11.7)	20 (12.1)	15 (9.1)	29 (12.9)	22 (9.8)
Renal and urinary disorders	7 (11.9)	7 (11.7)	16 (9.7)	18 (11.0)	23 (10.3)	25 (11.2)
Eye disorders	5 (8.5)	6 (10.0)	18 (10.9)	17 (10.4)	23 (10.3)	23 (10.3)
Psychiatric disorders	7 (11.9)	7 (11.7)	20 (12.1)	11 (6.7)	27 (12.1)	18 (8.0)
Cardiac disorders	4 (6.8)	0	15 (9.1)	12 (7.3)	19 (8.5)	12 (5.4)
Immune system disorders	3 (5.1)	3 (5.0)	7 (4.2)	4 (2.4)	10 (4.5)	7 (3.1)
Ear and labyrinth disorders	3 (5.1)	5 (8.3)	4 (2.4)	4 (2.4)	7 (3.1)	9 (4.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.7)	5 (8.3)	4 (2.4)	6 (3.7)	5 (2.2)	11 (4.9)
Hepatobiliary disorders	2 (3.4)	2 (3.3)	3 (1.8)	7 (4.3)	5 (2.2)	9 (4.0)
Endocrine disorders	3 (5.1)	2 (3.3)	1 (0.6)	4 (2.4)	4 (1.8)	6 (2.7)
Congenital, familial and genetic disorders	0	1 (1.7)	0	0	0	1 (0.4)
Product issues	0	0	1 (0.6)	0	1 (0.4)	0

Source: Table 3.03.

Notes: Only on-treatment data is displayed, see RAP Section 14.6.1.6 for definition. AEs are presented in descending order from the MedDRA SOC with the highest overall incidence across treatment groups. Where the overall incidence for any two or more AE SOCs are equal, the events are presented in alphabetical order. MedDRA version 22.0.

a. Subjects are counted only once per SOC.

Most common adverse events

Frequent AEs that occurred more commonly in the belimumab group and at an incidence at least 3% greater (total) than that observed with placebo were urinary tract infection (UTI) (15.6% placebo, 19.2% belimumab), cough (8.5% placebo, 12.5% belimumab) and abdominal pain upper (2.7% placebo, 6.3% belimumab).

Frequent AEs that occurred more commonly in the placebo group at an incidence at least 3% greater (total) than that observed in the belimumab group were arthralgia (14.7% placebo, 10.3% belimumab), gastroenteritis (11.2% placebo, 7.6% belimumab), anaemia (10.3% placebo, 5.4% belimumab) and SLE (5.4% placebo, 0.9% belimumab).

Table 37. Adverse Events Occurring in >=5%of Subjects (Total) by PT (Double-Blind, Safety Population)

	CYC/AZA		MMF		Overall	
Preferred Term[a]	Placebo N=59 n (%)	Belimumab 10 mg/kg N=60 n (%)	Placebo N=165 n (%)	Belimumab 10 mg/kg N=164 n (%)	Placebo N=224 n (%)	Belimumab 10 mg/kg N=224 n (%)
Any Event	54 (91.5)	56 (93.3)	157 (95.2)	158 (96.3)	211 (94.2)	214 (95.5)
Upper respiratory tract infection	12 (20.3)	14 (23.3)	58 (35.2)	58 (35.4)	70 (31.3)	72 (32.1)
Diarrhoea	12 (20.3)	13 (21.7)	33 (20.0)	29 (17.7)	45 (20.1)	42 (18.8)
Urinary tract infection	11 (18.6)	9 (15.0)	24 (14.5)	34 (20.7)	35 (15.6)	43 (19.2)
Headache	11 (18.6)	11 (18.3)	24 (14.5)	19 (11.6)	35 (15.6)	30 (13.4)
Nasopharyngitis	13 (22.0)	11 (18.3)	16 (9.7)	20 (12.2)	29 (12.9)	31 (13.8)
Arthralgia	11 (18.6)	6 (10.0)	22 (13.3)	17 (10.4)	33 (14.7)	23 (10.3)
Cough	4 (6.8)	10 (16.7)	15 (9.1)	18 (11.0)	19 (8.5)	28 (12.5)
Nausea	9 (15.3)	9 (15.0)	15 (9.1)	13 (7.9)	24 (10.7)	22 (9.8)
Gastroenteritis	1 (1.7)	9 (15.0)	24 (14.5)	8 (4.9)	25 (11.2)	17 (7.6)
Hypokalaemia	3 (5.1)	3 (5.0)	17 (10.3)	19 (11.6)	20 (8.9)	22 (9.8)
Herpes zoster	5 (8.5)	4 (6.7)	14 (8.5)	15 (9.1)	19 (8.5)	19 (8.5)
Rash	5 (8.5)	8 (13.3)	12 (7.3)	12 (7.3)	17 (7.6)	20 (8.9)
Anaemia	7 (11.9)	3 (5.0)	16 (9.7)	9 (5.5)	23 (10.3)	12 (5.4)
Leukopenia	6 (10.2)	6 (10.0)	13 (7.9)	10 (6.1)	19 (8.5)	16 (7.1)
Bronchitis	2 (3.4)	5 (8.3)	15 (9.1)	11 (6.7)	17 (7.6)	16 (7.1)
Vomiting	3 (5.1)	4 (6.7)	13 (7.9)	12 (7.3)	16 (7.1)	16 (7.1)
Back pain	4 (6.8)	3 (5.0)	12 (7.3)	12 (7.3)	16 (7.1)	15 (6.7)
Dizziness	6 (10.2)	4 (6.7)	12 (7.3)	9 (5.5)	18 (8.0)	13 (5.8)
Pyrexia	3 (5.1)	3 (5.0)	14 (8.5)	8 (4.9)	17 (7.6)	11 (4.9)
Hypertension	6 (10.2)	4 (6.7)	8 (4.8)	9 (5.5)	14 (6.3)	13 (5.8)
Muscle spasms	4 (6.8)	6 (10.0)	8 (4.8)	9 (5.5)	12 (5.4)	15 (6.7)
Fatigue	5 (8.5)	5 (8.3)	10 (6.1)	6 (3.7)	15 (6.7)	11 (4.9)
Oedema peripheral	6 (10.2)	3 (5.0)	6 (3.6)	10 (6.1)	12 (5.4)	13 (5.8)
Abdominal pain	3 (5.1)	2 (3.3)	10 (6.1)	9 (5.5)	13 (5.8)	11 (4.9)
Pneumonia	2 (3.4)	2 (3.3)	11 (6.7)	9 (5.5)	13 (5.8)	11 (4.9)
Insomnia	4 (6.8)	4 (6.7)	9 (5.5)	6 (3.7)	13 (5.8)	10 (4.5)
Dyspepsia	2 (3.4)	2 (3.3)	12 (7.3)	6 (3.7)	14 (6.3)	8 (3.6)
Abdominal pain upper	0	4 (6.7)	6 (3.6)	10 (6.1)	6 (2.7)	14 (6.3)
Acne	1 (1.7)	2 (3.3)	7 (4.2)	10 (6.1)	8 (3.6)	12 (5.4)
Oedema	1 (1.7)	3 (5.0)	11 (6.7)	5 (3.0)	12 (5.4)	8 (3.6)
Pain in extremity	2 (3.4)	6 (10.0)	6 (3.6)	6 (3.7)	8 (3.6)	12 (5.4)
Systemic lupus erythematosus	6 (10.2)	0	6 (3.6)	2 (1.2)	12 (5.4)	2 (0.9)

Source: Table 3.05.
Notes: Only on treatment data is displayed, see RAP Section 14.6.1.6 for definition.AEs are presented in descending order from the MedDRA PT with the highest overall incidence across treatment groups. If the overall incidence for any two or more adverse event PTs are equal, the events will be presented in alphabetical order. MedDRA version 22.0.
a. Subjects are counted only once per PT.

Open-label extension phase

During the procedure, the MAH submitted final results from the open-label extension. A summary of the adverse events is provided in Table 38.

Table 38. Adverse Events Summary in Open-label Phase (Safety Open-label Population)

	CYC/AZA			MMF			Overall		
At least one:	Placebo to Belimumab 10 mg/kg N=27 n (%)	Belimumab 10 mg/kg to Belimumab 10 mg/kg N=30 n (%)	Total N=57 n (%)	Placebo to Belimumab 10 mg/kg N=96 n (%)	Belimumab 10 mg/kg to Belimumab 10 mg/kg N=102 n (%)	Total N=198 n (%)	Placebo to Belimumab 10 mg/kg N=123 n (%)	Belimumab 10 mg/kg to Belimumab 10 mg/kg N=132 n (%)	Total N=255 n (%)
AE	20 (74.1)	20 (66.7)	40 (70.2)	56 (58.3)	72 (70.6)	128 (64.6)	76 (61.8)	92 (69.7)	168 (65.9)
Related AE	9 (33.3)	8 (26.7)	17 (29.8)	16 (16.7)	16 (15.7)	32 (16.2)	25 (20.3)	24 (18.2)	49 (19.2)
Serious AE	1 (3.7)	2 (6.7)	3 (5.3)	4 (4.2)	8 (7.8)	12 (6.1)	5 (4.1)	10 (7.6)	15 (5.9)
Severe AE	1 (3.7)	1 (3.3)	2 (3.5)	5 (5.2)	4 (3.9)	9 (4.5)	6 (4.9)	5 (3.8)	11 (4.3)
AE resulting in IP discontinuation and/or withdrawal from study	0	0	0	1 (1.0)	4 (3.9)	5 (2.5)	1 (0.8)	4 (3.0)	5 (2.0)
All Deaths	0	0	0	1 (1.0)	0	1 (0.5)	1 (0.8)	0	1 (0.4)

Serious adverse event/deaths/other significant events

Serious adverse events

An overview of serious adverse events is presented in Table 35.

Serious AEs by SOC were similar between treatment groups in the overall population (29.9% placebo, 25.9% belimumab; with the highest incidence in infections and infestations (17.0% placebo, 13.8% belimumab).

During the first 24 weeks of treatment, there were 24 and 27 serious infections in placebo [in 20 (8.9%) subjects] and belimumab [in 19 (8.5%), subjects], respectively. Post Week 24 (80-week maintenance phase), subjects reported fewer events in both treatment groups with 19 and 13 serious infections in placebo [18 (9.2%) subjects] and belimumab [12 (6.1%) subjects], respectively.

The overall rates of serious infections in BEL114054 were higher than observed in the pooled SLE population; however, this was driven by the events within the first 24 weeks of treatment (while subjects are receiving intensive induction of LN remission therapy). The rate of serious infections during the maintenance phase of BEL114054 was comparable to the rates observed in the pooled SLE studies.

Four subjects in the belimumab group experienced SAEs associated with Grade 4 (laboratory toxicity) neutropenia: 2 events of febrile neutropenia and 2 events of pancytopenia. One subject with pancytopenia had received 2 doses of induction therapy with CYC after which the total leukocyte and neutrophil counts decreased prior to receiving belimumab and prior to the onset of pancytopenia. Neutropenia has been reported in patients with SLE (20% to 40%) with severe neutropenia reported in cases (0.8% to 4%) in those treated with CYC, AZA or MMF and patients with SLE [Carli, 2015[28]]. Additionally, in BEL114054 subjects with stable Grade 3 neutropenia or stable Grade 3 leukopenia were permitted to enrol in the study, if they were not receiving CYC at screening. All cases of neutropenia in BEL114054 were confounded by the concurrent use of CYC, AZA, or MMF in the setting of underlying neutropenia associated with the disease under study.

Deaths

A total of 11 deaths (including off-treatment deaths) occurred during the double-blind phase, 5 (2.2%) subjects in the placebo group and 6 (2.7%) in the belimumab group (Table 35). In 7 subjects (4 belimumab and 3 placebo) these fatal SAEs occurred while on study treatment. In the remaining 4 subjects, the fatal SAEs occurred post treatment (2 placebo, 2 belimumab).

A summary of the deaths is provided in Table 39.

Infections was the most common cause of death in both groups, including 2 possibly related to belimumab:

- the first case was a 63-year-old woman with concomitant CYC who developed pancytopenia and a bacterial pneumonia 14 days after the first dose of Benlysta. Abnormalities reported in bone marrow could be a result of a possible synergic effect of cyclophosphamide and Benlysta, but firm conclusions of the role of Benlysta cannot be drawn.

- the second case was a 49-year-old women from Taiwan. Sixty (60) days after the first dose of belimumab and 4 days after the most recent dose, she was admitted to the ICU with severe bilateral pneumonia. Pathogens proved by BAL and sputum examinations included Mycobacterium tuberculosis, pneumocystis jirovecii, cytomegalovirus, and throat swab was also positive for Influenza A. Sputum culture grew Pseudomonas aeruginosa. Treatment was given against TB, influenza, CMV, pneumocystis

[28] Carli L, Tani C, Vagnani S, Signorini V, Mosca M. Leukopenia, lymphopenia, and neutropenia in systemic lupus erythematosus: Prevalence and clinical impact—A systematic literature review. *Seminars in Arthritis and Rheumatism* 45(2015)190–94.

jiroveci and bacterial pneumonia. In response to CHMP's request, the MAH confirmed that TB testing was not performed in this case.

Table 39. Listing of Deaths by Preferred Term and Adjudicated Category

Treatment Group	Subject ID (Age [years]/Sex/Race/Country)	Preferred Term/ Adjudicated Death Category	Relation to Study Agent	Days Since Dose First/Last
Fatal SAE started on-treatment although death may have occurred anytime thereafter				
Placebo	(36/F/Black or African American/Brazil)	Pneumonia/ Infectious	No	17/17
	(33/F/Black or African American/Brazil)	Encephalopathy/ Unknown	Yes	70/13
	(57/F/White/Argentina)	Sepsis/ Infectious	Yes	156/16
Belimumab	(63/F/White/Mexico)	Pneumonia[a]/ Infectious	Yes	14/14
	(49/F/Asian/Taiwan)	Pneumonia/ Infectious	Yes	61/5
	(38/F/White/Argentina)	Dyspnea (hypertension)/ Unknown	Yes	123/4
	(54/F/White/Russian Federation)	Pneumonia/ Vascular	No	512/36
Fatal SAE started off-treatment				
Placebo	(21/F/Black or African American/US)	Hemorrhage intracranial/ Infectious	No	692/447
	(29/F/Asian/ Philippines)	Seizure/ Unknown	Yes	82/85
Belimumab	(56/F/White/Brazil)	Septic shock/ Infectious	No	240/240
	(26/F/Asian/Philippines)	Cardiac failure congestive/ SLE related	No	135/107

Note: All subjects in MMF subgroup with the exception of (*) subject that was in CYC subgroup.
a. Subject serious events also included bone marrow toxicity and pancytopenia.
CYC = Cyclophosphamide.
F = Female.
MMF = Mycophenolate mofetil.
SLE = Systemic lupus erythematosus.
US = United States.

In the 28-week open-label extension phase, there was one additional death 85 days after the first open-label infusion in a patient switching from placebo to belimumab. This was a 35-year-old female in the MMF subgroup and the death was associated with a fatal SAE of multiple organ dysfunction syndrome, sepsis secondary to healthcare associated pneumonia, and chronic kidney disease.

Adverse events of special interest

Given the potential risks associated with immune modulating therapeutic proteins as well as data from previously completed studies, a group of AESI were pre-specified: malignant neoplasms, post-infusion/anaphylaxis/hypersensitivity reactions, all infections of special interest, and depression/suicide/self-injury. A summary of AESI in study BEL114054 and completed SLE studies are shown in Table 40.

Table 40. Adverse Events of Special Interest in BEL114054, Completed Belimumab SLE Studies, and BEL115467 (Belimumab Large Safety Study)

	Number (%) of Subjects									
	BEL114054 (On-treatment)						Pooled IV + SC (excluding BEL115467)		BEL115467-IV (On-Treatment Period)	
	CYC/AZA		MMF		Overall					
At least one event	PBO (N=59)	BEL 10 mg/kg (N=60)	PBO (N=165)	BEL 10 mg/kg (N=164)	PBO (N=224)	BEL 10 mg/kg (N=224)	PBO IV +SC (N=1355)	BEL IV + SC (All doses) (N=2815)	PBO (N=2001)	BEL 10 mg/kg (N=2002)
Malignancies Excluding NMSC[a]	0	0	0	2 (1.2)	0	2 (0.9)	2 (0.1)	7 (0.2)	5 (0.2)	5 (0.2)
Post-Infusion/Injection Systemic Reactions (PISR) per CMQ Broad Search[a,c]	9 (15.3)	10 (16.7)	20 (12.1)	16 (9.8)	29 (12.9)	26 (11.6)	106 (7.8)	281 (10.0)	-[b]	-[b]
All Infections of Special Interest[a]	8 (13.6)	7 (11.7)	26 (15.8)	23 (14.0)	34 (15.2)	30 (13.4)	91 (6.7)	163 (5.8)	50 (2.5)	36 (1.8)
Serious	0	3 (5.0)	7 (4.2)	6 (3.7)	7 (3.1)	9 (4.0)	16 (1.2)	38 (1.3)	17 (0.8)	17 (0.8)
Depression (inc. mood disorders and anxiety)/Suicide/Self-injury[a]	5 (8.5)	3 (5.0)	11 (6.7)	8 (4.9)	16 (7.1)	11 (4.9)	88 (6.5)	198 (7.0)	-[b]	-[b]
Serious Suicide/Self-injury[d]	0	0	0	1 (1.6)	0	1 (0.4)	4 (0.3)	4 (0.1)	5 (0.2)	11 (0.5)

Note: Subjects only counted once per category. Only treatment-emergent AEs are summarized.
MedDRA version 22.0

a. Per Custom MedDRA query.
b. Non-serious events in these AESI categories were not collected in BEL115467.
c. Serious PISR are not shown due to differences in summary outputs between BEL114054 and BEL115467 ISS (pooled IV + SC and BEL115467).
d. Per Standard MedDRA query.

Malignant neoplasms

There were no malignancies reported in the placebo group. Three subjects (1.3%) in the belimumab group (during on-treatment phase) experienced malignancies: one case each of basal cell carcinoma (AZA maintenance period), papillary thyroid cancer (MMF), and thymoma (MMF). The papillary thyroid cancer (T1a R/O N1a) occurred 159 days after the first dose of belimumab + MMF and was treated with a total thyroidectomy. The thymoma (type B/type 1) occurred 1 year and 118 days after the first dose of belimumab + MMF and was a low-grade hyperplasia that was conservatively adjudicated as a malignancy. According to the MAH, no clinically meaningful differences were observed for any malignant neoplasm category.

Infections of special interest

Infections of special interest included: opportunistic infections, herpes zoster (HZ), tuberculosis and sepsis (all and serious). In general, there were no clinically relevant differences observed between the treatment groups in the overall safety population and by induction/maintenance subgroup.

A slightly higher number of serious infections of special interest was observed during the first 24 weeks of treatment in both treatment arms (2.2% placebo, 3.1% belimumab), which was likely due to intensive immunosuppressive therapy and high doses of corticosteroids. Serious infections of special interest decreased (1.0% placebo and 1.0% belimumab) during the maintenance phase (post Week 24) of the study.

Regarding herpes zoster, there were no clinically meaningful differences in the incidence of HZ events between treatment groups overall (8.5% placebo, 9.4% belimumab), during the first 24 weeks (4.5% placebo, 5.8% belimumab) or post Week 24 (5.6% placebo, 4.1% belimumab).

Although the incidences of HZ were higher in this study compared to those observed in the pooled SLE studies (4.0% placebo, 3.6% belimumab), the incidence of HZ in the belimumab group was within the range (6.5% to 11.2%) described in literature in studies most closely aligned with BEL114054 in terms of follow-up and patient demographics [Mok, 2019[29]; Park, 2019[30]; Houssiau, 2010[31]].

The main risk factors for HZ in SLE and LN have been described as exposure to corticosteroids, immunosuppressive drugs including oral and IV CYC, renal impairment, and lymphopenia [Chen, 2011; Hu, 2016; Singh, 2016]. Multiple reports have described increased incidence of HZ in patients treated with MMF. A study in LN showed a higher frequency of HZ infection (18%) during the first 6 months of treatment with MMF vs 3% in patients treated with tacrolimus [Mok, 2016[32]]. Opportunistic infections and HZ (disseminating and recurrent) are expected in the SLE patient population, in association with the use of background immunosuppressant medications, and have been reported in LN patients being treated with MMF.

The MAH concludes that the observed frequencies in this study of all events of HZ (serious, opportunistic and disseminated) are in line with published data for HZ infection in LN.

Laboratory findings

Haematology parameters

The total percentage of subjects with either a Grade 3 or Grade 4 value post-baseline were generally similar between the belimumab and placebo groups for each haematology parameter, except that a slightly higher proportion of subjects in the belimumab group had a Grade 3 value neutrophils (2.7% placebo, 3.6% belimumab).

Events of Grade 4 neutropenia were balanced overall and between the induction regimens for the 8 subjects (4 belimumab, 4 placebo) that had their laboratory results reported by central laboratory. Two additional belimumab subjects developed Grade 4 neutropenia during AZA maintenance. In 4 out of the 6 belimumab subjects with Grade 4 neutropenia, treatment with belimumab was resumed and the subjects remained in the study. Given the small numbers, the presence of confounding medications and the underlying disease state, these cases were considered not to be causally related to belimumab and clinically meaningful differences were not seen.

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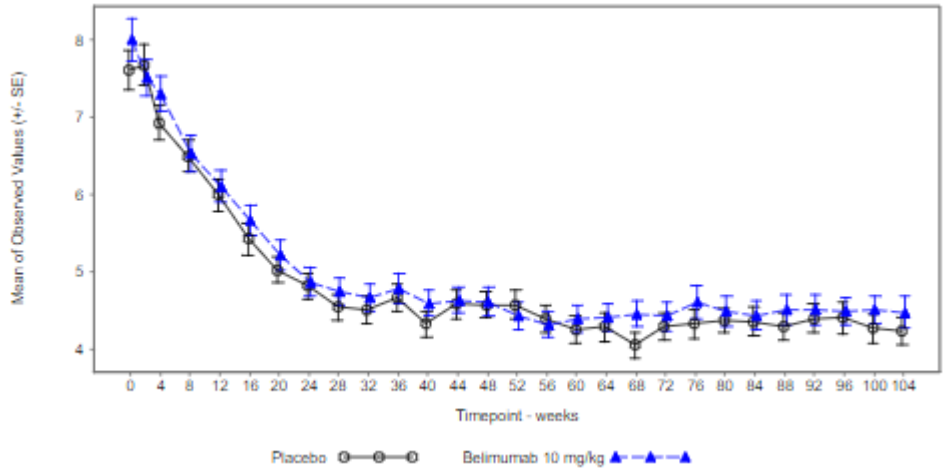

Figure 28. Neutrophils (10^9/L)

Immunoglobulins

Two subjects; one placebo and one belimumab (both in the MMF subgroup), had IP withdrawn as a result of a Grade 4 IgG, with no obvious signs of infection noted.

Immunogenicity

Belimumab has a low propensity for inducing anti-drug antibodies. None of the 224 belimumab-treated subjects confirmed positive for anti-belimumab antibodies.

Safety in special populations

A total of 8 pregnancies were reported during the double-blind phase of study BEL114054. Five pregnancies were in subjects receiving placebo: 4 resulted in live births and1 resulted in a spontaneous abortion. Three pregnancies were reported in subjects receiving belimumab: 2 resulted in an elective abortion, 1 subject was lost to follow-up. No congenital anomalies were reported.

Safety related to drug-drug interactions and other interactions

The large molecular weight of belimumab precludes it from being metabolized by the cytochrome P450 system. Thus, the types of drug interactions that occur between 1 or more drugs that compete for metabolism by this family of enzymes are not expected with belimumab. For these reasons, nonclinical drug interaction studies were not considered relevant for belimumab. Also, since belimumab is a monoclonal antibody with high specificity, no nonclinical studies were undertaken to examine potential pharmacodynamic drug interactions.

Discontinuation due to adverse events

The incidence of AEs resulting in IP discontinuation were the same between the treatment groups (12.9% in both treatment groups). Infections and infestations were the most common AEs leading to IP discontinuation: overall (4.5% in both treatment groups), in the CYC/AZA subgroup (1.7% placebo, 3.3% belimumab) and in the MMF subgroup (5.5% placebo, 4.9% belimumab).

Post marketing experience

Benlysta has been approved since 2011 for use in the treatment of patients with active, autoantibody-positive SLE who are receiving therapy. Although not approved for LN, as of 06 Mar 2020 there were 11 SAEs reported when using Benlysta off-label for a LN indication. There were no trends detected in the types of events reported and all were consistent with the known safety profile of Benlysta.

This section discusses the post marketing experience with the current registered SLE indication. The cumulative post-marketing exposure to belimumab is estimated to be 83,577 patient years based on data from IQVIA through 31 December 2018. This estimate reflects exposure to both the IV formulation (78,427 patient years) and the SC formulation (5150 patient years).

Routine pharmacovigilance is ongoing for belimumab. In addition, the EU Risk Management Plan specifies risk minimization measures including ongoing surveillance of important identified and potential risks. Based on headline results for study BEL115467, GSK recategorized depression and suicidality from a potential risk to an identified risk. The other identified risks are hypersensitivity and infusion or injection-related systemic reactions, and infections. Potential risks are PML, malignancies, immunogenicity, and effects on immunizations, including interactions with live vaccines. Areas requiring confirmation or further investigation include pregnancy outcomes, the use of belimumab in elderly patients, severe active CNS lupus and investigation into SLE patients with severe LN.

Two belimumab registries are ongoing. HGS1006-C1124 (BEL116543/SABLE) is a 5-year prospective observational registry to assess adverse events of interest and effectiveness in adults with active, autoantibody-positive SLE treated with or without Benlysta (belimumab). The Benlysta Pregnancy Registry is a prospective cohort study. The primary objective of this registry is to evaluate pregnancy and infant outcomes following Benlysta exposure and health status of live born infants at 1 year.

A cumulative and periodic report of post-marketing surveillance was submitted as scheduled in the belimumab Periodic Benefit-Risk Evaluation Report dated 08 May 2019, which covers the reporting period from 09 March 2018 to 08 March 2019.

2.5.1. Discussion on clinical safety

The cumulative exposure to belimumab (both IV and SC formulations) post-marketing is 108,447 patient years. The safety profile of Benlysta includes infections, hypersensitivity and infusion/injection-related systemic reactions, and psychiatric events including depression and suicidality. Potential risks listed in the RMP include PML, malignancies, immunogenicity, and effects on immunizations.

A total of 448 subjects with LN were randomized in study BEL114054 (224 in each group), all of whom received at least 1 dose of study drug and constitute the safety population.

The mean (SD) duration of exposure to study agent in the BEL114054 mITT population was 546.4 (251.3) days for placebo and 577.3 (243.5) days for belimumab. The median (range) duration of exposure was 726.0 (28 to 748) days in the placebo group and 727.0 (28 to 743) days in the belimumab group.

Adverse events

The incidence of subjects experiencing at least 1 AE in the overall population was 94.2% in the placebo group and 95.5% in the belimumab group. The most common adverse event SOC was infections and infestations, with the most common adverse event being upper respiratory tract infection.

Serious adverse events and deaths

Serious AEs occurred in 29.9% of the patients in the placebo group and 25.9% of the patients in the belimumab group. In the subgroup of patients treated with CYC/AZA, the frequency of AEs and SAEs was slightly higher for belimumab than compared to placebo, however there were few patients in this subgroup hampering firm conclusions.

There were 11 deaths in the study (5 placebo, 6 belimumab). The incidence of deaths in BEL114054 was higher (2.2% placebo and 2.7% belimumab) compared to the incidence observed in the pooled SLE studies (0.4% placebo, 0.6% belimumab). According to the MAH, this is consistent with literature where the risk of mortality in LN (6- to 6.8-fold) is higher than SLE (2.4-fold) when compared to general population which could be attributed to a higher frequency of co-morbidities, frequent use of potent immunosuppressants and HDCS as well as higher disease activity. This is agreed on by CHMP.

Infections was the most common cause of death in both groups. This is consistent with the known safety profile of Benlysta, and not surprising because treatment was given on top of intense immunosuppression. There were 2 cases of deaths due to infections possibly related to belimumab.

The first death occurred in a patient with concomitant CYC who developed pancytopenia and a bacterial pneumonia 14 days after the first dose of Benlysta. Abnormalities reported in bone marrow could be a result of a possible synergic effect of cyclophosphamide and Benlysta, but firm conclusions of the role of Benlysta cannot be drawn.

The second death was reported in a patient who presented severe bilateral pneumonia 60 days after the first dose of belimumab and 4 days after the most recent dose. Pathogens proved by BAL and sputum examinations included Mycobacterium tuberculosis, pneumocystis jirovecii, cytomegalovirus, and throat swab was also positive for Influenza A. Sputum culture grew Pseudomonas aeruginosa. Treatment was given against TB, influenza, CMV, pneumocystis jiroveci and bacterial pneumonia. Upon the CHMP's request, the MAH confirmed that TB testing was not performed in this case. The risk for reactivation of latent TB was thoroughly discussed in the latest PSUSA where it was concluded that no recommendation on latent TB screening was needed in section 4.4 of the SmPC. Furthermore, the patient was positive for pneumocystis jiroveci. Patients with LN are at high risk for pneumocystis jiroveci pneumonia (PCP) and there is support in literature for prophylactic treatment of patients treated with cyclophosphamide. The MAH was asked to discuss whether PCP prophylaxis with pentamidine inhalations should be recommended for LN patients treated with Benlysta, both in combination with CYC and MMF. The MAH provided further details on the case of PCP reported in study BEL114054. Furthermore, a review of company's safety database revealed 11 additional reports of PCP. According to the MAH, all of the cases of PCP received for patients concurrently receiving belimumab from both clinical trial and spontaneous sources were significantly confounded by the severity of the disease, levels of intense immunosuppression and high dose corticosteroid use, and there are no evidence for a causal relationship between PCP and the use of belimumab. The MAH concluded that there is insufficient evidence to support a SmPC update to include PCP prophylaxis recommendations for LN patients treated with Benlysta. This is agreed on by the CHMP.

In the 28-week open-label extension phase, there was one additional death (multiple organ dysfunction syndrome, sepsis secondary to healthcare associated pneumonia, and chronic kidney disease) 85 days after the first open-label infusion in a patient switching from placebo to belimumab.

Infections are known side effects of Benlysta treatment, and there are no new safety signals observed in these data.

AESIs

Pre-specified AESIs were malignant neoplasms, post-infusion/anaphylaxis/hypersensitivity reactions, all infections of special interest, and depression/suicide/self-injury. Although there was an imbalance in cases of malignancies with 2 cases both occurring in the Benlysta arm and the cases occurred after a reasonable latency, there were few cases and no conclusions can be drawn. According to the MAH, there

were no malignancies reported during the open-label phase. Serious infections of special interest (including herpes zoster) were slightly more frequent for Benlysta than for placebo during the first 24 weeks. CHMP agrees with the MAH that the observed frequencies of herpes zoster are in line with published data for HZ infection in LN patients.

Laboratory values

A slightly higher proportion of subjects in the belimumab group had a Grade 3 value neutrophils (2.7% placebo, 3.6% belimumab). However, when looking at the actual values, there are no important difference between the arms. Events of Grade 4 neutropenia were balanced between the arms.

Although there was a case of death due to pneumonia and pancytopenia, overall there seems to be no clinically meaningful increase in risk for neutropenia for belimumab than compared to placebo. Leukopenia is listed in Section 4.8 of the SmPC. This is considered acceptable to the CHMP.

No Benlysta-treated patient developed ADAs.

Long-term data in the LN population are limited. The MAH clarified that no additional pharmacovigilance activities will be performed in LN patients. Spontaneous cases received with a reported indication of LN will be documented in future reviews including signal evaluations, and PSURs. This was agreed by CHMP since even though the safety in patients with severe LN and intense concomitant treatment might differ from the non-LN population, no new safety concerns were identified from the available data in LN patients (104-week double-blind phase plus 28 weeks open-label extension).

The safety data presented from study BEL114054 is overall consistent with the known safety profile of Benlysta, with an increased risk for infections and fatal infections. The current population of LN patients are more fragile than the overall SLE population due to severe organ involvement and concomitant heavy immunosuppression, and an increased risk for infections and death than compared to the overall SLE population was observed in the study. Nonetheless, given the high unmet medical need for the LN population at an increased risk for organ failure and death, these risks are accepted. Section 4.8 of the SmPC is updated with summary of safety data in LN patients (most common ADRs) and incidences of infections, serious infections and fatal infections.

2.5.2. Conclusions on clinical safety

The safety data presented from study BEL114054 is overall consistent with the known safety profile of Benlysta in the SLE population, with an increased risk for infections and fatal infections. LN patients are more fragile than the overall SLE population due to severe organ involvement and concomitant heavy immunosuppression. However, given the high unmet medical need in the LN population at an increased risk for organ failure and death, the safety profile of Benlysta in the treatment of patients with LN is found acceptable to the CHMP.

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 with this application.

The PRAC considered that the risk management plan version 39 is acceptable. The CHMP endorsed the Risk Management Plan version 39 with the following content:

Important Identified Risks		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Infections	Routine risk minimisation measures: SmPC Sections 4.4, 4.8 This is a prescription only medicine. Additional risk minimisation measures None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire on infections for patients 5 to 11 years old. • Analysis of additional safety data that may arise from ongoing studies, including serious infections and infections of special interest from ongoing open-label study BEL114055 in the pediatric population. • Evaluation of data on serious infections including opportunistic infections, tuberculosis, and herpes zoster from long-term safety registry (BEL116543/SABLE) Additional pharmacovigilance activities: • None
Psychiatric events including depression and suicidality	Routine risk minimization measures: SmPC Sections 4.4, 4.8 This is a prescription only medicine. Additional risk minimization measures: DHPC distribution in April 2019.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Analysis of additional safety data that may arise from ongoing studies • Specific adverse reaction follow-up questionnaires for Depression and Suicidality: Belimumab and Possible Suicidal Behavior/Suicidal Ideation (Including Potential Self Harm such as Intentional Overdose) Additional pharmacovigilance activities: • Prospective assessment of suicidality in randomised controlled trials and BEL116543/SABLE (5-year registry study)

Important Potential Risks		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Progressive Multifocal Leukoencephalopathy	Routine risk minimization measures: **The IV and SC SmPC** Routine activity includes appropriate labelling. Section 4.4 Special warnings and precautions for use of the SmPCs contains the EMA SmPC text agreed: Progressive multifocal leukoencephalopathy (PML) has been reported with Benlysta treatment for SLE. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded. This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted Follow-up Questionnaire for PML • Analysis of additional safety data that may arise from ongoing studies • Evaluation of data on opportunistic infections, including PML, tuberculosis, and herpes zoster from long-term safety registry (BEL116543/SABLE) Additional pharmacovigilance activities: None
Malignancies	Routine risk minimization measure: SmPC Section 4.4 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Analysis of additional safety data that may arise from ongoing studies • Evaluation of data on malignancies, including haematological malignancies and NMSC from years 2 through 5 of a large safety study (BEL115467/BASE) and long-term safety registry (BEL116543/SABLE) Additional pharmacovigilance activities: None

Missing Information		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Limited data in pregnant and lactating patients	Routine risk minimization measures: SmPC Section 4.6, 5.3 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Analysis of additional safety data that may arise from ongoing studies Additional pharmacovigilance activities: • Ongoing Benlysta Pregnancy Registry in selected countries where belimumab is marketed
Limited data in elderly patients	Routine risk minimization measures: SmPC Section 4.2, 5.2 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Evaluation of safety and efficacy data from ongoing and future studies Additional pharmacovigilance activities: • Analysis plan for BEL116559 has been agreed with EMA
Limited data on long-term safety in paediatric patients	Routine risk minimization measures: SmPC Section 4.2 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Additional pharmacovigilance activities: • Evaluation of safety (adverse events of special interest, including infections, other autoimmune disease, immunogenicity, and malignancies) and efficacy data from these studies including follow-up of enrolled subjects in BEL114055 until 10 years after their first belimumab dose • SLE paediatric studies with EMA in IV and SC PIP
Lack of data in SLE patients with severe active CNS lupus	Routine risk minimization measures: SmPC Section 4.4, 5.1 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • none Additional pharmacovigilance activities: • none

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 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the proposed changes are limited and not considered to significantly affect the readability of the package leaflet. No change to the layout is proposed.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

SLE is a heterogeneous chronic autoimmune inflammatory disease. Renal involvement is present in an average of 38% of patients at the time of SLE diagnosis and occurs in 40-70% of SLE patients during the course of their disease. SLE patients that are more likely to develop renal disease are typically of younger age, male and African, Asian or Hispanic. Approximately 10-20% of patients progress to ESRD within 10-15 years since LN diagnosis. LN is the most common and severe systemic manifestation of SLE that remains the most significant cause of morbidity and mortality. The location of immune complex deposition as confirmed by renal biopsy, defines the different histopathological classes of LN according to the Renal Pathology Society Working Group and the International Society of Nephrology Working Group (ISN/RPS Criteria from 2003) classification and informs the LN management and prognosis.

LN manifestations range from minimal proteinuria and microscopic haematuria to nephrotic range proteinuria, urinary casts, severe hypertension, peripheral oedema, and renal insufficiency or acute renal failure. Typical disease course of LN is characterized by episodes of flares interspersed between periods of disease quiescence.

Mortality is highest amongst SLE patients with proliferative renal involvement (Classes III and IV) and progression to renal failure is strongly predictive of mortality.

3.1.2. Available therapies and unmet medical need

Current approaches to the management of LN continue to rely on high dose corticosteroids (HDCS) and broad-spectrum immunosuppressive agents. First line standard therapies include CYC and HDCS for induction followed by AZA for maintenance or MMF and HDCS for induction followed by MMF for maintenance. Despite the aggressive nature of treatment, management of LN remains unsatisfactory. More than 60% of patients fail to achieve remission and up to 25% of patients in remission experience relapse. Suboptimal disease control results in irreversible nephron loss and progression to ESRD within 10-15 years of LN diagnosis. In addition to the challenges presented by the severity of the disease, cumulative exposure to potent non-selective immunosuppressants and corticosteroid burden are associated with significant side effects, long-term toxicities and organ damage accrual.

3.1.3. Main clinical studies

Study BEL114054 was a Phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled, 104-week study to evaluate the efficacy and safety of IV belimumab 10 mg/kg plus standard of care compared to placebo plus standard of care in adult SLE patients with active LN (histological classes III, IV, V or V in combination with III or IV LN).

All subjects received background therapy consisting of one of the following standard of care regimens:

- HDCS + CYC for induction therapy followed by Azathioprine (AZA) for maintenance therapy

  OR

- HDCS+ MMF for induction therapy followed by MMF for maintenance therapy

The primary efficacy endpoint was the PERR at Week 104 measured as a dichotomous response (Responder vs. Non-Responder). A responder is defined as urine protein to creatine ration (uPCR) ≤0.7 and eGFR is no more than 20% below pre-flare value or ≥60 mL/min/1.73m^2 and Not a Treatment Failure.

"Not a treatment failure" equals to patients who did not take protocol prohibited or restricted medication or dose specified in the protocol as:

- New immunosuppressant agents (other than as part of the induction and maintenance regimens).
- Corticosteroid use outside of the limits.
- Other investigational agents (biologic or non-biologic). Investigational applies to any drug not approved for sale in the country in which it is being used.
- Anti-TNF therapy (eg, adalimumab, etanercept, infliximab).
- Other biologics (eg, rituximab, abatacept, interleukin-1 receptor antagonist [anakinra]).
- IVIG.
- Plasmapheresis.

The 4 major secondary efficacy endpoints were: CRR at Week 104, PERR at Week 52, Time to Death or Renal-related Event, and ORR at Week 104.

A total of 446 patients were included in the study (n=223 in each arm).

3.2. Favourable effects

The primary endpoint, PERR at week 104, was achieved by 72/223 patients (32.3%) in the placebo group and 96/223 patients (43%) in the belimumab group (OR=1.55, 95% CI: 1.04-2.32, p value for difference between belimumab and placebo=0.03).

Among secondary endpoints, CRR at the same timepoint was achieved by 44/223 patients (19.7%) in the placebo group and 67/223 patients (30%) in the belimumab group (p value for difference between belimumab and placebo =0.0167). PERR at 52 weeks was achieved by 79/223 patients (35.4%) in the placebo group and 104/223 (46.6%) in the belimumab group (p value for difference between belimumab and placebo =0.02). Renal-related event or death occurred in 63/223 patients (28.3%) in the placebo group and 35/223 patients (15.7%) in the belimumab group (HR 0.51, 95% CI 0.34-0.77, p value for difference between belimumab and placebo =0.001).

3.3. Uncertainties and limitations about favourable effects

No data are available in patients with class I or II nephritis. Study BEL114054 did not include patients with class I or II nephritis whereas Benlysta is proposed for LN patients in combination with MMF or cyclophosphamide, which is not applicable for LN class I and II. The MAH argued that in the pivotal SLE studies, where patients with class I and II nephritis were eligible for inclusion i.e. Benlysta was given to patients with high disease activity despite standard therapy. However, the pivotal SLE studies were not designed to study the efficacy in the specific subgroup of class I and II LN patients. The MAH agreed upon the CHMP's request to revise the indication to patients with **active** lupus nephritis where treatment with background immunosuppressives is considered.

The efficacy in the pre-specified subgroup analysis of renal biopsy class V on the primary endpoint PERR was not shown. However, a trend for reduced risk of renal-related event or death was observed in this subgroup, CHMP agrees that class V LN patients could benefit from treatment with Benlysta in addition to SOC. Furthermore, the efficacy is most prominent in the subgroup of patients treated with concomitant MMF, and the difference for Benlysta vs placebo is smaller in the subgroup of patients treated with concomitant cyclophosphamide. Hence, the CHMP agreed that class V should be included in the indication. Subgroup analyses results are included in Section 5.1 of the SmPC.

There were many protocol amendments made throughout the study, including change of primary endpoint that raised concerns on the study reliability. The original study primary endpoint of ORR including urinary sediment and calculated GFR at Week 104 (IPD/TF/WD=NR; Van Elteren test) was included as a pre-planned sensitivity analysis. The results favoured belimumab but were not statistically significant. Thus, this change had an impact on the outcome of the study, in favour of the sponsor. The changes to the primary endpoint were thoroughly reviewed as part of the clinical efficacy assessment. The timing for the changes to the primary endpoint and their impact on the study reliability were discussed. The MAH confirmed that these changes were made prior to unblinding of the study results. All changes were agreed with EMA before implementation and made prior to unblinding of the study results. Therefore, the CHMP concluded that these changes were not data-driven but motivated from a clinical and statistical point of view and therefore did not affect study results reliability.

3.4. Unfavourable effects

The incidence of subjects experiencing at least 1 AE in the overall population was 94.2% in the placebo group and 95.5% in the belimumab group. The most common adverse event SOC was infections and infestations, with the most common adverse event being upper respiratory tract infection.

Serious AEs occurred in 29.9% of the patients in the placebo group and 25.9% of the patients in the belimumab group. In the subgroup of patients treated with CYC/AZA, the frequency of AEs and SAEs was slightly higher for belimumab than compared to placebo, however there were few patients in this subgroup (placebo n=59, belimumab n=60).

There were 11 deaths in the study (5 placebo, 6 belimumab). One additional death in a belimumab-treated patient occurred during the open-label extension phase. Infections were the most common cause of death in both groups. The current population of LN patients are more fragile than the overall SLE population due to severe organ involvement and concomitant heavy immunosuppression, and an increased risk for infections and fatal infections than compared to the overall SLE population was observed in the study. Nonetheless, given the high unmet medical need for the LN population at an increased risk for organ failure and death, these risks are accepted.

3.5. Uncertainties and limitations about unfavourable effects

Long-term data in the LN population are limited. CHMP agreed that monitoring through routine pharmacovigilance in the post marketing setting is sufficient since no new safety concerns were identified from the available safety data.

There was one case of death in a woman with bilateral pneumonia where pathogens proved by BAL and sputum examinations included Mycobacterium tuberculosis and pneumocystis jirovecii. This patient had not been screened for TB. No SmPC update was deemed necessary since the risk for reactivation of latent TB was reviewed in the latest PSUSA where it was concluded that no recommendation on latent TB screening was needed in section 4.4 of the SmPC. Furthermore, patients with LN are at high risk for PCP and there is support in literature for prophylactic treatment of patients treated with cyclophosphamide. A review of the MAH's safety database where 11 additional reports of PCP were identified indicated that the cases were significantly confounded by the severity of the disease, levels of intense immunosuppression and high dose corticosteroid use. The CHMP agreed with the MAH's conclusion that there are no evidences for a causal relationship between PCP and the use of belimumab and that there is insufficient evidence to support a SmPC update.

3.6. Effects Table

Table 41 Effects Table for Benlysta in Lupus Nephritis (data cut-off: 25 Jul 2019).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PERR	Primary efficacy renal response week 104	N (%)	96/223 (43)	72/223 (32.3)	Partial response. Treatment should aim at complete response.	Table 26 , Study BEL114054
CRR	Complete renal response week 104	N (%)	67/223 (30)	44/223 (19.7)		Table 26, Study BEL114054
Renal-related event or death	Death, end-stage renal disease, doubling of serum creatinine, renal worsening or renal-related treatment failure	N (%)	35/223 (15.7)	63/223 (28.3)		Table 26, Study BEL114054
Unfavourable Effects						
AE	Adverse event	N (%)	214/224 (95.5)	211/224 (94.2)		Table 35, Study BEL114054
SAE	Serious adverse event	N (%)	58/224 (25.9)	67/224 (29.9)		Table 35, Study BEL114054
Death	All deaths	N (%)	6/224 (2.7)	5/224 (2.2)		Table 35, Study BEL114054

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The aim of treatment for LN is to achieve complete renal response. This has been shown to be associated with a favourable long-term renal prognosis in the context of RCTs and long-term observational studies, and therefore, is considered the ultimate therapeutic goal in LN (Kostopoulou, Curr Rheum Rep 2020 22:30[27]).

According to the EMA Guideline (EMA/CHMP/51230/2013 corr 1), studies conducted in patients with LN should be aimed for the control of renal activity with **complete renal response** recommended as primary endpoint. The primary endpoint chosen in the pivotal study BEL114054, PERR which is a **partial response** differs from the EMA Guideline recommendation. A partial response could possibly have been accepted by the CHMP if assessed at an earlier timepoint, however, at 104 weeks, the CHMP considers that the treatment should aim for remission. Therefore, the efficacy assessment focused also on the secondary endpoint of complete renal response (CRR).

The primary endpoint, PERR, was achieved by a higher proportion of patients in the belimumab group than compared to the placebo group. The difference is statistically significant. Also, the clinically more relevant secondary endpoint of CRR was achieved by a higher proportion of patients in the belimumab group than compared to the placebo group.

The primary endpoint was changed several times throughout the ongoing study. The changes to the primary endpoint while the study was ongoing were thoroughly discussed during the procedure. The MAH clarified that the revisions to the study protocol were agreed with EMA before their implementation, that all changes to the primary endpoint were made prior to unblinding of the study results and that no laboratory parameters were unblinded prior to unblinding of the study. Therefore, CHMP concluded that the changes to primary endpoint were not data driven but motivated from a clinical and statistical point of view and therefore did not affect the study results reliability.

No data are available in patients with class I or II nephritis from Study BEL114054 since patients with class I or II nephritis were not included. However, in the pivotal SLE studies, where patients with class I and II nephritis were eligible for inclusion, Benlysta was given to patients with high disease activity despite standard therapy. During the procedure, the MAH agreed to revise the indication to specify that Benlysta should only be given to patients with **active** nephritis, and in combination with background immunosuppressive therapy.

In the pre-specified subgroup analysis of renal biopsy class, no or very limited increased efficacy was observed for belimumab compared to placebo for patients with a pure membranous nephritis (class V). A trend for reduced risk of renal-related event or death was observed in this subgroup. Hence, the CHMP agreed that class V can be included in the indication. Furthermore, the efficacy was most prominent in patients treated with background MMF than CYC. The results in these important pre-specified subgroups are clearly reflected in section 5.1 of the SmPC.

The safety data presented from study BEL114054 is overall consistent with the known safety profile of Benlysta, with an increased risk for infections and fatal infections. The incidence of deaths in BEL114054 was higher (2.2% placebo and 2.7% belimumab) compared to the incidence observed in the pooled SLE studies (0.4% placebo, 0.6% belimumab). The targeted LN population is more fragile than the overall SLE population due to severe organ involvement and concomitant heavy immunosuppression. However, given the high unmet medical need in the LN patient population at an increased risk for organ failure and death, the safety profile in the LN patients is found acceptable to the CHMP.

3.7.2. Balance of benefits and risks

There is a high unmet medical need for new treatments in patients with LN.

The results from study BEL114054 show a statistically significant and clinically relevant effect for belimumab when it comes to primary and all major secondary endpoints. The efficacy was demonstrated when Benlysta is used in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis and was most prominent in the subgroup of patients treated with background MMF, and in patients with histopathological class III/IV nephritis.

The safety in the current population shows the same pattern as the known safety profile of Benlysta, but with an increased risk for death than compared to the overall SLE population. This is expected in the fragile LN population with severe organ involvement and heavy concomitant immunosuppression.

Exposure comparisons between IV dosing and SC dosing based on simulations from population PK models are the justification for the change of the SC posology for the treatment of LN patients. The benefit-risk balance for the 400 mg Q1W to week 4 followed by 200 mg Q2W posology is considered unchanged compared to the 10 mg/kg IV posology since the average concentration is comparable between SC and IV dosing.

3.7.3. Additional considerations on the benefit-risk balance

The adequacy of a separate, LN indication which is a severe manifestation of SLE was questioned during the assessment since Benlysta is already approved in the treatment of SLE patients while considering the CHMP´s principles of wording of the indication (EMA/CHMP/483022/2019) foreseeing that if a study population is already covered by the already approved indication, an extension of the indication in section 4.1 of the SmPC is not accepted. However, the current indication for SLE, *"Benlysta is indicated as add-on therapy in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti- dsDNA and low complement)* ***despite standard therapy*** *(see section 5.1*)" does not apply to LN, since in LN, Benlysta is indicated for use as ***first-line therapy in combination with intensive immunosuppressants***. Thus, due to the different places in therapy for Benlysta in SLE and LN respectively, a separate LN indication is agreed by CHMP.

3.8. Conclusions

The overall B/R of Benlysta is positive in the following indication:

Benlysta is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis (see sections 4.2 and 5.1).

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	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult patients with active lupus nephritis for belimumab in combination with background immunosuppressive therapies; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 39 of the RMP is agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes 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 'Benlysta-H-C-002015-II-0080'

Attachments

1. SmPC Package Leaflet (changes highlighted) as adopted by the CHMP on 25 March 2021.