Module 1.8.2

European Union Risk Management Plan (EU-RMP) for Benlysta (Belimumab)

RMP version to be assessed as part of this application	
RMP Version number	46.2
Data lock point for this RMP	08 March 2024
Date of final sign off	9 April 2025

Rationale for submitting an updated RMP

RMP version 46.2 is being submitted to update the SLE SC pediatric dosing regimen to 3 weight bands and to clarify the SC pediatric SLE indication extension is relevant only for the prefilled pen. RMP version 46.2 tracked changes are highlighted in turquoise, RMP version 46.1 tracked changes are highlighted in yellow and RMP version 46 tracked changes are highlighted in green.

RMP version 46.1 is being submitted to update the belimumab ATC code. RMP version 46.1 replaces RMP v46.0 and contains all proposed changes submitted in RMP version 46.0 (eCTD sequence 0321) submitted previously under procedure EMA/H/C/002015/II/0133. RMP version 46.0 tracked changes are highlighted in green and RMP version 46.1 tracked changes are highlighted in yellow.

RMP version 46 provides an update to expand the current belimumab pediatric SLE indication to include the subcutaneous formulation following completion of Parts A and B of study 200908, an open-label, single treatment arm study to evaluate the pharmacokinetics, safety, and pharmacodynamics of SC belimumab plus standard therapy in pediatric participants 5 to 17 years of age. GSK has also taken the opportunity to update the data lock point (DLP) to 08 March 2024, which includes updates to event and incidence rates of the safety concerns, pregnancy information and exposure data. Other changes were made for accuracy, consistency and in line with GVP V rev 2 guidance which do not impact the key safety information.

Summary of significant changes in this RMP:

PART	MODULE	Changes made in EU-RMP version 46
I		Added row and text for "Important information about its composition". Update to indication and dosage (current and proposed). Addition of subtitles. Updated ATC code.
II	SI.1.2	Updated to align with current treatment recommendations.
II	SI.1.3	Minor updates
II	SI.1.4	Minor updates
II	SII	Amalgamation to reduce duplicative text and other minor update for clarity and consistency.
II	SIII.1	Addition of 200908 study and minor clarification to BEL115467 study. Updates to the number of ongoing and current studies and investigational indications.
II	SIII.2	Clinical trial exposure updated due to updated DLP

II	SIV.1	Table 6: • Updates to rationale column for patients with severe active lupus nephritis and patients with malignant neoplasm. • Removal of 200908 from long-term safety in patients less than 18 years of age (not designed to study long-term safety). • Updates to missing information classification made for consistency with list of safety concerns.
II	SIV.2	Exposure data updated due to updated DLP
II	SIV.3	Table 7: Updates to exposure details of Pregnant and Breastfeeding women (due to updated DLP) and exposure for children and patients of different weights.
II	SV.1.2	Table 8: Post-Marketing exposure updated due to updated DLP.
II	SVII.3.1	Presentation of important identified risks and important potential risks updated including event and incidence rates (due to updated DLP). PML data updated due to DLP. Preventability text updated for identified and potential risks of Infections and PML to summarize existing SmPC language. Missing information of limited data on long-term safety in pediatric patients updated to remove study 200908 (not designed to study long-term safety).
II	SVII.3.2	Missing information of limited information on pregnant and breastfeeding women updated due to DLP.
III	III.2	Summary added for PLUTO (BEL114055) study for consistency with existing list of additional pharmacovigilance activities.
III	III.3	Completed milestones removed. Clarification to title of study BEL114055.
V	V.1	Table 9: Text updated for routine RMM of potential risk of PML to summarize existing SmPC Section 4.4 language.
V	V.3	Table 10: Text updated for routine RMM of potential risk of PML to summarize existing SmPC Section 4.4 language. Missing information of limited data on long-term safety in pediatric patients updated to remove study 200908.
VI	I	Indication updated
VI	II.B	Text updated for routine RMM of potential risk of PML. Missing information of limited data on long-term safety in pediatric patients updated to remove study 200908.
VI	II.C.2	Summary added for PLUTO (BEL114055) study for consistency with existing list of additional pharmacovigilance activities.

Annex 2		Table 11: Added study BEL116559 for consistency with existing list of additional pharmacovigilance activities. Clarification to title of study BEL114055. Table 12: Study 114256 CSR sequence number and submission date added.
Annex 7		References updated.
Annex 8		EU RMP version 46 updates added. EU RMP version 46.2 updates added.

Other RMP versions under evaluation Not applicable		
Details of the currently approved RMP		
Version number	Approved with procedure	Date of approval (opinion date)
45.1	EMA/H/C/002015/II/0116	11 April 2024

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV
QPPV Signature	Electronic signature on file

Abbreviations

ACE	angiotensin-converting enzyme
aCL	anti-cardiolipin
ACR	American College of Rheumatology
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ANA	antinuclear antibodies
AST	aspartate transaminase
ATC Code	Anatomical Therapeutic Chemical Classification System
AVSD	Atrioventricular septal defect
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte stimulator
BPR	Belimumab Pregnancy Registry
BR3	BLyS receptor 3
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMV	Cytomegalovirus
CNS	central nervous system
CRD	controlled repeat dose
CSR	clinical study report
cSLE	childhood-onset SLE
CTD-ILD	Connective Tissue Disease associated Interstitial Lung Disease
CVA	cerebrovascular accident
DLP	Data lock point
DMC	Data Monitoring Committee
ECL	Electrochemiluminescence
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EU-RMP	European Union – Risk Management Plan
EUROCAT	European Surveillance of Congenital Anomalies
GDS	Global Datasheet
GGT	gamma glutamyl transferase
gm	Gram
GSK	GlaxoSmithKline
HBV	hepatitis B virus
HCP	health care provider
HCV	hepatitis C virus
HGS	Human Genome Sciences, Inc.
HIV	human immunodeficiency virus
HMG CoA	3-hydroxy-3-methyl-glutaryl-CoA
hr	Hour
HR	hazard ratio
HSR	hypersensitivity reaction
IB	Investigator's Brochure

ICD-9	International Classification of Diseases, 9th Revision
Ig	immunoglobulin
IM	Intramuscular
IMGN	Idiopathic Membranous Glomerulonephropathy
INBD	Impact National Benchmark Database
INN	International Nonproprietary Name
IUD	intrauterine device
IV	Intravenous
kg	Kilogram
LFT	Liver function tests
LMP	Last menstrual period
LN	Lupus nephritis
NHL	Non-Hodgkin's lymphoma
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	Minute
ml	Milliliter
mm	Millimeter
MMF	mycophenolate mofetil
NA	not applicable
NMSC	non-melanoma skin cancer
OTIS-MTB	Organization of Teratology Information Services/MotherToBaby
PASS	Post-authorization Safety Study
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PML	Progressive Multifocal Leukoencephalopathy
POAP	Pregnancy Outcomes Advisory Panel
PSUR	Periodic Safety Update Report
PT	prothrombin time
PTT	partial thromboplastin time
PY	patient years
RA	rheumatoid arthritis
SAE	Serious adverse event
SAC	Scientific Advisory Committee
SC	Subcutaneous
SELENA	Safety of Estrogen in Lupus National Assessment Trial
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Cooperating Clinics
SmPC	Summary of Product Characteristics
SOC	system organ class
SRI	SLE responder index
SRT	Safety Review Team
SSc-ILD	Systemic Sclerosis associated Interstitial Lung Disease
TACI	transmembrane activator-1 and calcium modulator and cyclophilin ligand-interactor

TNF	tumor necrosis factor
UCLH	University College London Hospitals
UK	United Kingdom
URTI	upper respiratory tract infection
UTI	urinary tract infection
USA	United States of America
US	United States
vs.	Versus
VSD	Ventricular Septal Defect
wk	Week

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Benlysta
LymphoStat-B

Trademarks not owned by the GlaxoSmithKline group of companies
None

TABLE OF CONTENTS

LIST OF ANNEXES

PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Belimumab
Pharmacotherapeutic group(s) (ATC Code)	L04AG04
Marketing Authorization Holder/ Applicant	GlaxoSmithKline (Ireland) Limited
Medicinal products to which this RMP refers	Belimumab
Invented name(s) in the European Economic Area (EEA)	Benlysta
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Belimumab is a human, IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.
	Summary of mode of action In vitro and in vivo studies of belimumab have demonstrated its ability to bind BLyS and inhibit its activity, while animal models and ex-vivo data collected from SLE patients suggest that elevated BLyS levels may be associated with the pathogenesis of SLE. In cynomolgus monkeys, belimumab has been shown to significantly reduce B cell representation in lymphoid tissue after 1 month of treatment and reduce peripheral blood B cells after 3 months

	of treatment. The ability of belimumab to reduce B cells has prompted the development of belimumab as a therapeutic monoclonal antibody for the reduction of B lymphocyte activity in patients with autoimmune disease.
	Important information about its composition Belimumab is a human IgG1λ antibody that recognizes soluble human BLyS. It comprises 2 heavy and 2 light chains, the variable portions of which were excised from belimumab single chain antibodies and recombinantly transferred into a single vector to yield a human monoclonal antibody, belimumab.
Reference to the Product Information	Please refer to proposed Product Information in Module 1.3.1.
Indication(s) in the EEA	Current: IV Product Belimumab 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. Belimumab is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis. SC Product Belimumab is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., anti-dsDNA and low complement) despite standard therapy. Belimumab is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis.

	Proposed: IV Product Belimumab 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. Belimumab is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis. <u>SC Product – prefilled pen</u> Belimumab 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., anti-dsDNA and low complement) despite standard therapy. Belimumab is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis. <u>SC Product – prefilled syringe</u> Belimumab is indicated as add-on therapy in adult patients 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. Belimumab is indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis.

Dosage in the EEA	Current: **Intravenous (IV) Product** In patients with SLE or active lupus nephritis, the recommended dosage regimen is 10 mg/kg by intravenous infusion on Days 0, 14 and 28, and at 4-week intervals thereafter. Belimumab should be infused over a 1-hour period. The patient's condition should be evaluated continuously. Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of belimumab. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reaction. In patients with SLE, discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. In patients with active lupus nephritis, belimumab should be used in combination with corticosteroids and mycophenolate or cyclophosphamide for induction, or mycophenolate or azathioprine for maintenance. <u>Transition from intravenous to subcutaneous administration</u> <u>*SLE*</u> If a patient with SLE is being transitioned from belimumab intravenous administration to belimumab subcutaneous administration, the first subcutaneous injection should be administered 1 to 4 weeks after the last intravenous dose.

	Lupus nephritis If a patient with lupus nephritis is being transitioned from belimumab intravenous administration to subcutaneous administration, the first dose of 200 mg subcutaneous injection should be administered 1 to 2 weeks after the last intravenous dose. This transition should occur any time after the patient completes the first 2 intravenous doses. **Subcutaneous (SC) Product** Posology *SLE* In patients with SLE, the recommended dosage regimen for SLE is 200 mg once weekly, administered subcutaneously. Dosing is not based on weight. The patient's condition should be evaluated continuously. Discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. *Lupus nephritis* In patients initiating therapy with belimumab for active lupus nephritis, the recommended dosage regimen is a 400 mg dose (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. In patients continuing therapy with belimumab for lupus nephritis, the recommended dosage is 200 mg once weekly. Belimumab should be used in combination with corticosteroids and mycophenolate or cyclophosphamide for induction, or mycophenolate or azathioprine for maintenance. The patient's condition should be evaluated continuously. SLE and LN Missed doses If a dose is missed, it should be administered as soon as possible. Thereafter, patients can

	resume dosing on their usual day of administration or start a new weekly schedule from the day that the missed dose was administered. <u>Changing the weekly scheduled dosing day</u> If patients wish to change their weekly dosing day, a new dose can be given on the newly preferred day of the week. Thereafter the patient should continue with the new weekly schedule from that day, even if the dosing interval may be temporarily less than a week.
	Proposed: **Intravenous (IV) Product** In patients with SLE or active lupus nephritis, the recommended dosage regimen is 10 mg/kg by intravenous infusion on Days 0, 14 and 28, and at 4-week intervals thereafter. Belimumab should be infused over a 1-hour period. The patient's condition should be evaluated continuously. Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of belimumab. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reaction. In patients with SLE, discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after 6 months of treatment. In patients with active lupus nephritis, belimumab should be used in combination with corticosteroids and mycophenolate or cyclophosphamide for induction, or mycophenolate or azathioprine for maintenance.

	Transition from intravenous to subcutaneous administration *SLE* If a patient with SLE is being transitioned from belimumab intravenous administration to belimumab subcutaneous administration, it is recommended that the first subcutaneous injection be administered 1 to 4 weeks after the last intravenous dose. *Lupus nephritis* If a patient with lupus nephritis is being transitioned from belimumab intravenous administration to subcutaneous administration, it is recommended that the first dose of 200 mg subcutaneous injection be administered 1 to 2 weeks after the last intravenous dose. This transition can occur any time after the patient completes the first 2 intravenous doses. **Subcutaneous (SC) Product** Posology *SLE* The patient's condition should be evaluated continuously. Discontinuation of treatment with belimumab is to be considered if there is no improvement in disease control after 6 months of treatment. *Adults*: Both the pre-filled pen and pre-filled syringe may be used to administer belimumab in adults. The recommended dosage regimen for SLE is 200 mg once weekly, administered subcutaneously. Dosing is not based on weight.

Children – pre filled pen:

Children and adolescents (aged 5 to less than 18 years). The recommended subcutaneous dose is based on weight

Body weight	Recommended dose
≥ 50 kg	200 mg once weekly
30 to < 50 kg	200 mg every 10 days
15 to < 30 kg	200 mg every 2 weeks

Children – pre filled syringe- :
In patients 5 years to less than 18 years of age, subcutaneous administration of Benlysta with the pre-filled syringe has not been evaluated and subcutaneous administration of Benlysta with the pre-filled pen is not recommended.

Lupus nephritis

Adults:

In patients initiating therapy with belimumab for active lupus nephritis, the recommended dosage regimen is a 400 mg dose (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. In patients continuing therapy with belimumab for active lupus nephritis, the recommended dosage is 200 mg once weekly. Belimumab is to be used in combination with corticosteroids and mycophenolate or cyclophosphamide for induction, or mycophenolate or azathioprine for maintenance. The patient's condition should be evaluated continuously.
If a patient with lupus nephritis is being transitioned from belimumab intravenous administration to subcutaneous administration, it is recommended that the first dose of 200 mg subcutaneous injection be administered 1 to 2 weeks after the last intravenous dose. This

	transition can occur any time after the patient completes the first 2 intravenous doses. Missed doses If a dose is missed, it is recommended be administered as soon as possible. Thereafter, patients can resume dosing on their usual day of administration or start a new schedule from the day that the missed dose was administered. Changing the scheduled dosing day If patients wish to change their scheduled dosing day, a new dose can be given on the newly preferred day of the week. Thereafter the patient can continue with the new schedule from that day, even if the dosing interval may be temporarily less than usual.
Pharmaceutical form(s) and strengths	Current: IV Product Powder for concentrate for solution for infusion. Each vial contains 120 mg or 400mg of belimumab. After reconstitution, the solution contains 80 mg belimumab per ml. SC Product Benlysta 200 mg solution for injection in pre-filled syringe. Each pre-filled syringe contains 200 mg of belimumab in 1 ml. Benlysta 200 mg solution for injection in pre-filled pen. Each pre-filled pen contains 200 mg of belimumab in 1 ml.
	Proposed (if applicable): There is no new proposed pharmaceutical form or strength.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SLE is a chronic debilitating autoimmune disease with a complex and multifactorial etiology. Individuals with SLE commonly experience a waxing and waning pattern of disease activity during the course of disease. SLE is characterized by the presence of elevated levels of autoantibodies, which directly damage the body's cells and tissues or form immune complexes which cause inflammation and tissue damage. A range of organ systems may be involved simultaneously or sequentially. The manifestations of SLE include arthritis, pleuritis, pericarditis, stroke, seizure, nephritis, anemia, thrombocytopenia, alopecia, photosensitivity, and malar rash. Over time, individuals with SLE are known to accrue irreversible organ damage, which contributes to an increased mortality rate compared to the general population.

LN is an inflammatory condition of the kidney caused by SLE. Overall, the basic pathological features of LN are similar to SLE. Typical disease course of LN is characterized by episodes of flares interspersed between periods of disease quiescence. Renal flares (proteinuric and nephritic) are associated with impaired renal prognosis and increased cumulative exposure of patients to drug toxic effects. Symptoms of LN range from mild asymptomatic proteinuria and/or microscopic hematuria with normal renal function, to severe nephrotic syndrome and/or acute renal failure. About half of LN patients will have reduced GFR, indicative or impaired renal function.

Regardless of age of onset or the time of diagnosis, SLE subjects share many immunogenetic and serologic similarities [Aggarwal, 2015; Barron, 1993; Livingston, 2012; Mina, 2013]. There is great variability in published literature on the magnitude of the discordance between childhood-onset SLE (cSLE) and SLE in adults regarding clinical and laboratory features at onset and over time, medications prescribed, and damage accrual [Mina, 2010]. Compared with adult SLE, cSLE-patients may have more active disease both at the time of diagnosis and over time [Kamphuis, 2010; Livingston, 2012; Mina, 2013]. cSLE can be associated with more rapid accrual of damage and may have a higher degree of morbidity compared with SLE in adult populations [Kamphuis, 2010; Levy, 2012; Malattia, 2013; Tucker, 2008]. Several studies suggest that glomerulonephritis is more prevalent in cSLE than adult-onset SLE [Amaral, 2014; Ambrose, 2016; Fish, 1977; King, 1977; Barron, 1993; Fonseca, 2018; Tarr, 2015]. In addition, cSLE patients have a significantly higher occurrence of neurological involvement at the time of diagnosis than adult-onset SLE patients [Fonseca, 2018; Tucker, 2008].

SI.1 Indication

INCIDENCE AND PREVALENCE OF SLE

Overall, the crude incidence rates of SLE across studies ranged from 2.0 [Tsioni, 2015] to 23.17 [Feldman, 2013] per 100,000 person-years, while the age- and gender-standardized incidence rates ranged from 2.9 [Jarukitsopa, 2015] to 7.22 [Furst, 2013] per 100,000

person-years. The median (25th percentile-75th percentile) of the crude incidence of SLE was 4.9 (3.5-5.6) per 100,000 person-years.

The crude incidence rates of SLE varied considerably across geographies, with the highest incidence rates (per 100,000 person-years) reported in the Americas (4.42-23.17), compared with Europe (2.0-4.91) and Asia (2.5-3.1). Across Europe, the crude incidence rate of SLE ranged from 2.0 [Tsioni, 2015] to 4.91 [Rees, 2016] per 100,000 person-years. Age- and gender-standardised incidence rate of SLE was reported only in the Spanish cohort study as 3.6 (95% CI: 3.0-4.2) per 100,000 person-years [Alonso, 2011].

The variation across and within regions may be due to differences in population (e.g., age, gender, race/ethnic composition), data source, study duration, or case ascertainment criteria for SLE.

Overall, the crude prevalence of SLE ranged from 19.5 [Ju, 2014] to 134 [Ferucci, 2014] per 100,000; while the age-standardized prevalence ranged from 17.5 [Alonso, 2011] to 178 [Ferucci, 2014] per 100,000. The crude SLE prevalence for Europe ranged from 36.7 [Brinks, 2014] to 97.0 [Rees, 2016] per 100,000. Age-standardized prevalence, reported in only one European study, is 17.5 per 100,000 [Alonso, 2011].

The wide variations in SLE prevalence across studies may be attributable to differences in factors such as study population, study design, data source, SLE definitions, and data source.

INCIDENCE AND PREVALENCE OF LN

The crude incidence rate of LN across studies ranged from 0.96 [Delarche, 2018] to 6.85 [Feldman, 2013] per 100,000 person-years, with median (25th percentile-75th percentile) of 1.1 (1.0-4.0) per 100,000 person-years. Only one study [Furst, 2013] reported age/gender- standardised- incidence rate (1.35 [95% CI: 1.14-1.55] per 100,000 person-years). Only one study [Delarche, 2018] was based on review of medical records of biopsy-proven LN patients and reported a lower incidence rate as compared to the two administrative database studies (0.96 vs.1.06 [Furst, 2013] and 6.85 [Feldman, 2013] per 100,000 person years).

Across studies, the percentage of LN in patients with SLE varied from 16.3% (adults; [Furst, 2013] to 21.5% in individuals aged 18-65 years [Feldman, 2013] to 37.4% in children [Hiraki, 2012]. The proportion of LN in adults with SLE was slightly lower than the pooled proportion of 29% (95% CI: 20-38%) biopsy-proven LN among SLE patients in a meta-analysis including 5 studies among adult or general population [Wang, 2018]. Overall, the median (25th percentile-75th percentile) of the proportion of LN in SLE patients was 21.5% (18.9%-29.5%). Based on two large US-based studies using data from public insurance for low-income individuals (Medicaid) and similar methods, prevalence per 100,000 varied from 3.64 in children [Hiraki, 2012] to 30.92 in adults [Feldman, 2013]; ~8.5-fold greater in adults than children. Consistent with the prevalence of SLE, overall prevalence of LN was lower in children than in adults, higher in females than in males, and higher in Asians and African-Americans than in Whites.

SI.1.1 Demographics of the population in the authorized indication and risk factors for the disease:

DEMOGRAPHICS AND RISK FACTORS FOR SLE

In European studies, the age of peak SLE prevalence varied across studies, and was one or two decades later in males than in females [Brinks, 2014; Rees, 2016]. Overall, the prevalence of SLE was higher in females than males and the female to male prevalence ratio ranged from 2.3:1 to 15.1:1. In Europe, female estimates ranged from 29.2 [Alonso, 2014] to 167.6 [Rees, 2016] per 100,000; male estimates ranged from 0 (Sardu, 2012) to 24.8 [Rees, 2016] per 100,000.

Prevalence data by race or ethnicity were provided in US studies, but not in European studies [Dall'Era, 2017; Feldman, 2013; Ferucci, 2014; Hiraki 2012; Housey, 2015; Izmirly, 2017; Lim, 2014; Somers, 2014]. Overall, a higher prevalence of SLE was observed in Asians and African-Americans than in Whites.

The incidence of SLE was higher in females than in males, with female to male incidence rate ratios (IRR) ranging from 2.1:1 [Brinks, 2016] to 14.5:1 [Flower, 2012]; though in general it ranged between 5:1 to 10:1 in most studies. In Europe, the incidence rate in females ranged from 1.9 [Brinks, 2016] to 8.34 [Rees, 2016] per 100,000 person-years and in males from 0.7 [Nightingale, 2017] to 1.44 [Rees, 2016] per 100,000 person-years. The age- and gender-standardised incidence rate was 3.6 (95% CI: 3.0-4.2; [Alonso, 2011]; age-standardised incidence rate of SLE was 1.1 (95% CI: 0.7-1.7) per 100,000 person-years for males and 5.9 (95% CI: 4.9-7.0) for females. European studies reported a range of female to male IRRs, varying from 2.1:1 [Brinks, 2016] to 7.7:1 [Nightingale, 2017].

DEMOGRAPHICS AND RISK FACTORS FOR LN

In general, the prevalence of LN increased with increasing age. Among US adults, prevalence increased from 24.92 per 100,000 in the 18–29-year age group to 42.79 per 100,000 in the 50-64 year- age group; [Feldman, 2013]. In the US pediatric population, prevalence was lower than in adults, but still showed an increased trend with age; from 0.17 per 100,000 in children aged 3 to <6 years to 7.32 per 100,000 in those aged 15 to <18 years; [Hiraki, 2012].

The prevalence of LN in females was ~4 times that in males in both adults (39.93 vs. 10.18 per 100,000; [Feldman, 2013] and children (5.97 vs. 1.34 per 100,000; [Hiraki, 2012].

The prevalence of LN by race/ethnicity was also reported by Feldman, 2013, and Hiraki, 2012. In Feldman, 2013 overall prevalence among US adults was ~4 times higher among African-Americans (59.69 per 100,000) and 3.6 times higher among Asians (56.56 per 100,000) compared to Whites (15.83 per 100,000). Likewise, in the US pediatric population, prevalence among Asians, African-Americans, and Whites was 11.21, 5.79, and 1.19 per 100,000 children, respectively [Hiraki, 2012]. Thus, the LN prevalence was ~9 times higher in Asians and ~5 times higher in African-Americans compared to Whites in the overall pediatric population.

Similar to the prevalence data, the incidence of LN was lower in children, higher in

females, and higher in Asians, Hispanics and African-Americans than in Whites.

SI.1.2 The main existing treatment options

Treatment Goals and Recommendations

The treatment goals in SLE are to improve long-term patient outcomes, including longer survival, prevent organ damage and optimize health-related quality of life by controlling disease activity and minimizing comorbidities and drug toxicity [van Vollenhoven, 2014; Fanouriakis, 2019]. Within the 2019 EULAR treatment recommendations for non-renal SLE**,** hydroxychloroquine (HCQ) is recommended in all patients with SLE unless contraindicated, at a dose not exceeding 5 mg/kg/day. Glucocorticoids (GCs) are the mainstay of treatment in SLE flares and result in rapid symptom relief when given as pulses of IV methylprednisolone 125 mg/day to 1000 mg/day for 1 to 3 days or high oral doses (>0.5 mg/kg/day). However, long-term therapy can have detrimental effects, including irreversible organ damage. Dose should therefore be reduced to ≤5 mg/day of prednisone equivalent or discontinued in the long-term. In patients not responding to HCQ (alone or in combination with GCs), or in patients unable to reduce GCs to maintenance doses, addition of immunosuppressive drugs or biologics is recommended. IS drugs [(such as methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CYC), cyclosporin, and tacrolimus] are added to GCs and HCQ to facilitate GC tapering and prevent disease flares. Belimumab is recommended in non-renal SLE patients with inadequate control following first-line treatments (typically including combination of HCQ with GC with or without IS agents), and where it is not possible to taper GC dose to acceptable levels. Rituximab (RTX) is recommended for patients with organ-threatening refractory disease and/or in patients with intolerance/contraindications to standard IS.

The treatment goals for LN patients include patient survival, long-term preservation of kidney function, prevention of disease flares, prevention of organ damage, management of comorbidities and improvement in health-related quality of life. High dose GCs combined with CYC or MMF are the current standard of care induction treatment regimens for active severe LN, and low-dose corticosteroids plus either AZA or MMF are 2 commonly used maintenance regimens to maintain the disease in remission [van Vollenhoven, 2014; Fanouriakis, 2020]. HCQ should be continued long-term. More recently, biologic agents such as RTX (off-label) and belimumab have been introduced for treatment for the treatment of non-responding/refractory LN.

The 2023 EULAR SLE treatment recommendations provide additional guidance on the early use of biologic therapy [Fanouriakis 2023, Boumpas, 2023] with the addition of immunomodulating/immunosuppressive agents (e.g., MTX, AZA, or MMF and/or biologic agents [e.g., belimumab or anifrolumab]) early on in patients with non-renal SLE. For active severe LN, additional therapy with belimumab or calcineurin inhibitors (such as voclosporin or tacrolimus, with MMF) should be considered early on during initial therapy and should continue for at least 3 years [Boumpas, 2023].

Real-world treatment patterns

In a targeted review of the literature of 7 studies [Collins, 2016; Schwarting, 2016; von Kempis, 2019; Hui-Yuen, 2015; Iaccarino, 2018; Ribi, 2014], glucocorticoids and antimalarials (both used as monotherapy or combination therapy with different drugs) were the most commonly used drug classes in SLE patients across countries (GCs, 48% to 100%; antimalarials, 53% to 92%). IS drug use ranged from 15% to 73% across studies. Overall, GCs were used in the majority of patients, often at higher-than-recommended doses. Among patients receiving biologics in US-based observational studies, IV belimumab was prescribed to 53%-77%. Not all studies provided data on non-steroidal anti-inflammatory drug (NSAID) use. Where reported, variability was high, ranging from 6% to 87%. Over a period of three years, the use of GCs declined by ~10% in both the US and the Canadian studies, whereas the findings are inconsistent for HCQ use (which increased in the Canadian study and declined in the US study).

The differential use of antimalarials, GCs, IS drugs and biologics across studies may stem from factors such as differences in study population (age, incident or prevalent disease, SLE severity, organ damage, hospitalized patients), study period, drug availability, cost of drugs, and geographical distribution (different guidelines used and different physician preferences). The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) or disease severity correlated with prescribing patterns, specifically for GCs.

Real-world use of belimumab in SLE

Real-world use of belimumab has been reported mostly in adult SLE patients with high disease activity or who are refractory to other standard-of-care treatments [Collins, 2019; Collins, 2016; Hui-Yuen, 2015; Ke, 2015; Marcondes, 2018]. Most patients showed clinical improvement as early as 6 months of belimumab treatment, and improvement continued through 24 months. Treatment with belimumab resulted in reduction in mean prednisone-equivalent dose of 2.9 mg (at 6 months) to 15.1 mg (at 24 months) across studies. Over a period of 24 months, the mean Safety of Estrogens in Lupus National Assessment (SELENA)-SLEDAI scores reduced from 12.3 at baseline to 4.5; the mean SLEDAI-2000 (SLEDAI-2K) scores reduced from 8.3 to 4.0 and the mean Disease Activity Score-28 joints (DAS-28) scores reduced from 4.2 to 1.8 across studies. Belimumab treatment led to reductions in both the mean number of flares and the number of patients with ≥1 flare over 24 months. Effectiveness results were generally consistent across subgroups (where assessed) such as patients with high disease activity, different ethnic groups, and childhood-onset SLE. Over a follow-up period of 6–24 months, 4%–33% discontinuations were reported in observational studies. Lack of efficacy, patient request and infections were the most common reasons. The proportion of patients discontinuing belimumab due to adverse events (AEs) was reported to be low. For example, in 501 patients enrolled in the US cohort study; OBServe, at 24 months only 2.8% of discontinuations were due to AEs.

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Progression of disease

In an international cohort [Chan, 2016], 31% of the SLE patients had LN at the time of enrolment; however, enrolment occurred up to 15 months (mean 6 months) following SLE diagnosis. In 4 other studies providing country-specific data (from Spain, France and China) the proportion of patients with LN at the time of SLE diagnosis was 7% to 26% [Huong, 1999; Mok, 1999; Siso, 2010; Galindo-Izquierdo, 2016].

The proportion of SLE patients developing LN over the course of their disease varied from 31% to 48%. Of the SLE patients that develop LN, ~80% to 90% develop LN within 5 years of diagnosis [Hanly, 2016b; Narvaez, 2017; Siso, 2010; Croca, 2011; Adler, 2006; Huong, 1999; Al Arfaj, 2009; Mok, 1999]. The risk of LN is greatest during the first few years; however, the risk may plateau up to 8 years following diagnosis. At least some of the variation across studies may be due to different methods of case ascertainment.

Male SLE patients appeared to be at higher risk of developing LN, with one study reporting a greater than 2-fold risk (odds ratio [OR]: 2.6, 95% confidence interval [CI]: 2.0-3.3). Patients who developed SLE at a younger age appeared to have a higher risk of developing LN (OR for those <16 vs. those 16-50 years at diagnosis: 2.5 [95% CI 4.3-8.6]; for those <16 vs. those ≥5 years, 6.1 (95% CI 1.9-3.3). Furthermore, patients of Hispanic, Asian and African ethnicity had a higher risk of LN than Caucasian patients [Hanly, 2016b].

Mortality

Overall mortality in SLE patients was 2-3 times that of the general population. The risk of mortality was significantly increased due to renal disease (~5 times), cardiovascular disease (CVD; ~2 times), and infection (~5 times) [Lee, 2016]. Mortality increases by 6-6.8 fold in patients with LN [Bernatsky 2006; Faurschou 2010; Lerang 2014; Yap 2012].

Mortality varied by geographical region/country, time period of study and patient population. Mortality rates ranged from 8.4 to 21 per 1000 patient-years in SLE patients across geographies. Survival was higher in Europe and Middle East and North Africa (MENA), and in more recent studies. [Gomez-Puerta, 2015; Jonsen, 2011; Kao, 2014; Lopez, 2012]

Survival for black patients (median 5-year survival: 73%, median 10-year survival: 66.5%) seemed to be lower than for Caucasians, Asians and Hispanics (median 5-year survival: >80%, median 10-year survival: >75%). The range in survival was wide for Caucasian patients, with the lowest 5-year survival rates published in old studies for the US (68.6%; [Kellum, 1964], and the highest in a German study (96.6%; [Manger, 2002]), and in relatively old studies for US (94%, in SLE patients excluding those with nephritis; [Wallace, 1981]), New Zealand (96%; [Hart, 1983]), and Spain (90%; [Blanco, 1998]).

Infections, CVDs and SLE disease activity were the most commonly reported causes of death. A systematic review of observational studies conducted by [Wang, 2015] included 36 studies for cause of death analysis, and showed that infection (33.2%), kidney disease (18.7%), lupus encephalopathy (13.8%), and CVD (11.5%) were the top 4 causes of death.

SI.1.4 Important co-morbidities

SLE patients usually have a high burden of pre-existing comorbidities at diagnosis, and the risk of development of multiple comorbidities after diagnosis is higher than in the general population or matched controls. Hypertension (16.9%-40.0%) and infections (36.0%-39.0%) are the most common comorbidities in the overall adult SLE population followed by cerebrovascular disease (3.3%-17.6%), heart failure (1.3%-17.6%), osteoporosis (7.6%-15.0%) and diabetes mellitus (2.7%-21.4%) [González, 2017; Hanly, 2016a; Jonsen, 2011; Torrente-Segarra, 2017; Kariburyo, 2020; Chan, 2016].

A cross-sectional multi-center study examined the prevalence of comorbidities among 2,926 SLE patients without secondary Sjgren's Syndrome in Spain [Ra-Figueroa, 2017]. The most common comorbidities were dyslipidemia (30%), hypertension (27%), and severe infection (17%). Additional comorbidities included osteoporotic fracture (5.7%), fibromyalgia (5.2%), cardiovascular events (8%), diabetes mellitus (4.2%), non-lymphoma cancer (4.1%), and lymphoma (0.4%) [Rúa-Figueroa, 2017]. The prevalence of comorbidities differed by patient sex in this population, with male patients statistically significantly more likely than female patients to exhibit dyslipidemia (39.1% versus 30.5%), high blood pressure (41.4% versus 28.0%), mild liver disease (12.1% versus 6.7%), chronic obstructive pulmonary disease (8.7% versus 2.1%), acute myocardial infarction (10.5% versus 2.8%), heart failure (7.2% versus 3.9%), pulmonary embolism (6.6% versus 3%), and peripheral artery disease (4% versus 2%; [Riveros Frutos, 2017]. On the other hand, female SLE patients had a higher prevalence of autoimmune thyroid disease than male patients (8.7% versus 3.9%; [Riveros Frutos, 2017]).

González & Alarcón (2017) recently reviewed the prevalence of CVD, malignancies, osteoporosis, and other comorbidities in SLE patients across seven different cohorts. The prevalence of experiencing any vascular event ranged from 3.5-8.1% in the three cohorts reporting this aggregated measure. Diabetes prevalence ranged from 1.0-4.7% (reported in all cohorts), infection prevalence ranged from 18.5-86.4% (reported in 3 cohorts), and any malignancy ranged from 2.2-8.0% (reported in 5 cohorts).

In pediatric patients, the relative risk (RR) of various comorbidities is also substantially higher in patients with SLE than in the general population. RRs are 2- to 5-fold higher for urinary tract infection (2.21), diabetes mellitus (2.58), osteoarthrosis (3.05), ischemic heart disease (IHD; 4.42), and solid tumors other than lymphoma (4.74); 8- to 9-fold higher for cerebrovascular disease (8.28) and glaucoma (9.01); and more than 10-fold higher for dyslipidemia (12.07), heart failure (13.98), osteoporosis including avascular necrosis (AVN; 17.96), cataract (18.53), lymphoma (22.82), hypertension (52.31), and renal failure (115.77).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Table 2 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity including: **Reproductive and Developmental toxicity:** No belimumab related microscopic changes were noted in the male or female reproductive tissues in the cynomolgus monkey 6 month repeat dose toxicity study receiving belimumab up to 50 mg/kg every 2 weeks. Nonclinical reproductive studies have been performed in pregnant cynomolgus monkeys receiving belimumab 150 mg/kg by intravenous infusion (approximately 9 times the anticipated maximum human clinical exposure) every 2 weeks throughout pregnancy (for 21 weeks) and belimumab treatment was not associated with direct or indirect harmful effects with respect to maternal toxicity, or developmental toxicity. Treatment-related findings were limited to detecting that belimumab crossed the placenta, and the expected reversible reduction of B cells in both dams and infants. B cell numbers recovered after the cessation of belimumab treatment by about 1-year post-partum in adult monkeys and by 3 months of life in infant monkeys; IgM levels in infants exposed to belimumab in utero recovered by 6 months of age. Belimumab was detected in the milk of female cynomolgus monkeys administered 150 mg/kg every 2 weeks, indicating that belimumab may be excreted into human milk.	Based on animal studies, belimumab may cross the placenta and cause reversible reduction of B cells and IgM in infants. Animal studies did not indicate direct or indirect harmful effects with respect to maternal toxicity or pregnancy. There are limited data on the use of belimumab in pregnant women. No formal studies have been conducted. Subjects who are pregnant or nursing are excluded from belimumab clinical trials. The BENLYSTA Pregnancy Registry (BPR/BEL114256/ HGS1006-C1101) has closed (see Section SVII.3.2). The ongoing Belimumab & Lupus Pregnancy Study (213928/bMUM) has replaced BEL114256/HGS1006-C1101 and will provide additional information on pregnancy outcomes following belimumab exposure and health status of infants through age 1 year. Immunoglobulin G (IgG) antibodies, including belimumab, can cross the placental barrier. Belimumab should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Women of childbearing potential should take precautions to avoid pregnancy while being treated with belimumab. If prevention of pregnancy is warranted, adequate contraception should be used while using belimumab and for at least 4 months after the last belimumab treatment. There are no data regarding the excretion of belimumab in human milk, or systemic absorption of belimumab after ingestion. However, because belimumab was excreted into the milk of cynomolgus monkeys and maternal antibodies are excreted in breast

Key Safety findings (from non-clinical studies)	Relevance to human usage
	milk, it is recommended that a decision should be made whether to discontinue breast-feeding or discontinue belimumab, taking into account the importance of breast-feeding to the infant and the importance of the drug to the mother.
Genotoxicity: No genotoxicity studies have been performed with belimumab. **Carcinogenicity:** No carcinogenicity studies have been performed with belimumab	No increase in malignancies has been seen to date in phase 2 or phase 3 clinical trials, nor in a large, 1-year, randomized, controlled safety study (BEL115467/BASE) or the completed 4-year post-treatment follow-up period. In addition, the cumulative malignancy rate across all belimumab completed SLE trials is comparable to the expected rate in SLE patients from the literature. The SABLE registry study to assess malignancy risk is underway.
General Safety pharmacology: (as applicable) **Cardiovascular:** No effects on cardiovascular function (including QTc) observed in cynomolgus monkey studies (up to 6 months in duration) receiving 50 mg/kg every two weeks. **Renal system:** No changes in serum chemistry or urinalysis (including serum and urine protein levels) or microscopic changes in the kidneys were observed in cynomolgus monkeys (up to 6 months in duration) receiving 50 mg/kg belimumab every two weeks. **Hepatotoxicity:** No elevations in liver transaminases or microscopic changes in the liver were observed in cynomolgus monkey studies (up to 6 months in duration) receiving 50 mg/kg every two weeks.	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Mechanisms for drug interactions: No drug interaction studies have been conducted as belimumab is cleared through cellular catabolism following nonspecific uptake by pinocytosis and is not metabolized by the cytochrome P450 (CYP450) system. Therefore, 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 Pro-inflammatory cytokines can suppress the expression and activity of certain CYP450 enzymes, and belimumab may thus affect exposure to other drugs by relieving the suppression of metabolizing enzymes. When the effect (suppression) of BLyS (10 to 10000 pg/mL) on the mRNA levels of CYPs 1A2, 2C8, 2C9 and 3A4 was evaluated using TaqMan in cultured human hepatocytes from two donors, no concentration dependent changes were observed after 48 hours in the mRNA levels of any of the CYPs tested. These data suggest belimumab is unlikely to alter the PK of co-medications whose clearance is dependent on CYP450 enzymes	No evidence for drug interactions detected in population PK analysis of phase 3 IV or SC populations. Concomitant use of mycophenolate mofetil, azathioprine, methotrexate, and hydroxychloroquine did not substantially influence the pharmacokinetics of belimumab administered intravenously or subcutaneously based on the results of the population pharmacokinetic analyses, neither did a wide range of other comedications (non-steroidal anti-inflammatory medications, aspirin, and HMG-CoA reductase inhibitors). Co-administration of steroids and ACE inhibitors resulted in a statistically significant increase of systemic clearance in the population pharmacokinetic analysis for intravenous administration, but not for subcutaneous administration belimumab. However, these steroid and ACE inhibitor effects (6% and 9% increase in central clearance, respectively) for belimumab administered intravenously were not clinically meaningful as their magnitude was well within the range of normal variability of clearance. None of the comedications tested had a meaningful impact on belimumab PK and no dose adjustment is necessary for the comedications tested.
Other toxicity-related information or data (as applicable) IV and SC Irritation: No belimumab treatment related macroscopic or microscopic findings of irritation were noted following IV or SC administration to cynomolgus monkeys.	In the clinical study in SLE patients with belimumab SC (BEL112341), the frequency of injection site reactions was 6.1% (34/556) and 2.5% (7/280) for patients receiving belimumab and placebo, respectively. These injection site reactions (most commonly pain, hematoma, erythema, pruritus, and induration) were mild to moderate in severity. The majority did not necessitate drug discontinuation. Injection site reactions (subcutaneous formulation only) is listed as an adverse reaction in the SmPC. Injection site/infusion reactions are collected in ongoing and completed studies.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1 Brief overview of development

The global clinical development program for belimumab was initiated with an intravenous (IV) formulation as intended route of administration; Marketing authorization for the IV formulation was achieved in 2011 based on two completed pivotal controlled repeat-dose studies of belimumab (IV) in subjects with SLE (HGS1006-C1056, HGS1006-C1057).

Given the safety and efficacy observed in patients with SLE receiving IV belimumab, development of a subcutaneous (SC) formulation was pursued as a second to market formulation allowing for a portable, patient self-administered drug as well as an alternative route of administration for patients with poor venous access. Marketing authorization for the subcutaneous (SC) formulation was achieved in 2017 based on a single pivotal controlled trial in subjects with SLE (BEL112341/HGS1006-C1115) using a prefilled syringe. A device bridging program was conducted to support the prefilled autoinjector, including a PK study to demonstrate comparable drug exposure (BEL117100). In addition, reliability of the autoinjector device was evaluated with respect to chronic real-life use in SLE patients (Study 200339).

The double-blind phase of study BEL115471 to evaluate the efficacy and safety of 10 mg/kg belimumab administered IV compared with placebo in adult black subjects with active SLE over a 52-week blinded period has completed. Associated with the approval of IV belimumab, GSK agreed with regulators to conduct this study. A total of 496 subjects (165 subjects in placebo group; 331 subjects in belimumab 10 mg/kg group) received at least 1 dose of study agent during the double-blind phase of the study. Within BEL115471, the safety profile of IV belimumab 10 mg/kg plus standard therapy was generally comparable with placebo plus standard therapy. In addition, IV belimumab 10 mg/kg plus standard therapy in adult SLE subjects of black race demonstrated an acceptable safety profile consistent with the known safety profile of IV belimumab 10 mg/kg plus standard therapy in adult SLE subjects. No new safety concerns following treatment with IV belimumab 10 mg/kg were identified in subjects of black race. Although not statistically significant for the primary endpoint, the data from BEL115471 have shown a favorable benefit-risk profile of IV belimumab 10 mg/kg as an add-on treatment to standard therapy in black subjects with active, autoantibody positive SLE across a number of clinical measures.

Subjects who completed the double-blind phase of BEL115471 were assessed for eligibility to participate in a 6-month extension phase during which they received open-label belimumab 10 mg/kg body weight by IV infusion every 28 days. The open label extension has completed. No new safety signals were observed in this open-label analysis, and the safety results were consistent with the known safety profile of belimumab 10 mg/kg IV. Overall, no trends of clinical concern were noted with regard to the incidences of AEs, including SAEs and AEs of special interest, over the course of this open-label analysis. The incidences of AEs were generally consistent with that expected in this SLE population. Belimumab 10 mg/kg IV was well tolerated as an add-on therapy to standard of care in the treatment of SLE in subjects of black race.

The double-blind phase (Part A) of study BEL114055 to evaluate the safety, efficacy and pharmacokinetics (PK) of belimumab plus background standard therapy in pediatric subjects ages 5 years to 17 years of age with active systemic SLE has completed. Part B and C of BEL114055 are ongoing, and pediatric patients will be followed for safety for up to 10 years after their first IV belimumab dose. This study was a requirement associated with the approval of IV Benlysta in adults and was the subject of an agreed Pediatric Investigation Plan (PIP). A total of 93 subjects (40 subjects in placebo group, 53 subjects in the belimumab 10 mg/kg group) received at least 1 dose of study agent during Part A (double-blind phase) of the study. Within the limits of the 1-year data analyzed to date, the benefit:risk profile of IV belimumab 10 mg/kg in pediatric SLE patients appears consistent with that of the adult patient population.

In addition, the double-blind phase of study BEL113750 a 52-week study evaluating the efficacy and safety of belimumab 10 mg/kg IV versus placebo in the treatment of subjects with systemic lupus erythematosus (SLE) located in Northeast Asia (China, Japan, and South Korea) has completed. A total of 705 subjects (235 subjects in placebo group, 470 subjects in belimumab 10 mg/kg group) received at least 1 dose of study agent during the double-blind phase of the study. The open-label continuation period of this study in SLE subjects in China has completed (N=424). In this study, IV belimumab 10 mg/kg plus standard SLE therapy demonstrated significant improvement in disease activity and was generally well-tolerated. Overall, the efficacy and safety results are consistent in the 3 pivotal adult IV studies of belimumab [Furie, 2011; Navarra, 2011; Zhang, 2018]. In study BEL114333 (N=142), which was a was a continuation study of belimumab plus standard of care in SLE subjects who completed the DB phase of the BEL113750 protocol in Northeast Asia, specifically in Japan and South Korea, or who completed the OL phase of the BEL112341 protocol in Japan, all subjects received belimumab 10 mg/kg IV infused over 1 hour every 28 days. Belimumab was well tolerated as an add-on therapy to standard of care in the treatment of SLE up to 6 or more years of treatment. No new safety signals were observed in this OL analysis, and the safety results are consistent with the known safety profile of 10 mg/kg belimumab IV.

BEL116027, an open-label, non-randomized, 52-week, post commitment study which evaluated the efficacy and safety of treatment holidays and rebound phenomenon after treatment with belimumab 10 mg/kg IV in SLE, has completed. Adults with SLE who received belimumab 10 mg/kg IV for ≥6 months were recruited from 4 open-label studies to three arms: treatment holiday (TH; 24-week belimumab withdrawal, reintroduction for 28 weeks); continuous belimumab (treatment control [TC]), and long-term discontinuation (LTD). Subjects in the TH or TC groups must have had low disease at screening. A total of 80 subjects were enrolled in the study. Of those, 39 subjects (48.8%) were enrolled in the LTD group, 29 (36.3%) in the TC group and 12 (15.0%) in the TH group. Although the sample size was small, temporary discontinuation of belimumab therapy did not appear to significantly increase the risk of SLE disease flare and / or rebound over a six-month period in patients who had achieved low disease activity on belimumab. In addition, there were no new safety findings in this study, and the results continue to support the favorable benefit-risk profile of belimumab.

BEL115467 was a multi-center, randomized, placebo-controlled, 52-week study to evaluate mortality and AESI in adults with active, autoantibody-positive SLE treated with

belimumab plus standard therapy vs. placebo plus standard therapy. The objectives of this study were to evaluate mortality and adverse events of special interest, including serious infections, opportunistic infections and, other infections of interest, non-melanoma skin cancers (NMSC), malignancies excluding NMSC, serious psychiatric events, suicidality, and serious infusion and hypersensitivity reactions, over 1 year and corticosteroid reduction during weeks 40 through 52. Initially, it was planned that approximately 5,000 subjects would be randomized to 1 of 2 treatment groups: belimumab 10 mg/kg (2,500 subjects) plus standard therapy or placebo (2,500 subjects) plus standard therapy. After the completion of 2 additional placebo-controlled trials, it was estimated, based on revised mortality estimates from a total of 5 completed Phase 2/3 belimumab trials in SLE, that mortality rates could be assessed with the same planned level of precision (95% confidence interval [CI] ±0.46%) with a total sample size of 4,000 subjects. A sample size reduction was proposed and agreed with the FDA and EMA regulatory authorities. In addition, the study was designed to continue to collect data in the subjects who discontinued study agent. Therefore, two study reporting periods were defined for analysis outputs: 'on treatment' (defined as first dose to last dose + 28 days [or death]) and 'on study' (includes on- and off-treatment data; defined as first dose to end of Week 52 study follow-up [or death]). The overall safety profile demonstrated in study BEL115467 continued to support a favorable benefit:risk profile of belimumab. On-treatment all-cause mortality was similar between belimumab 10 mg/kg and placebo with more off-treatment deaths observed in the placebo group. The rates of serious infections, and opportunistic infections and other infections of interest were similar between treatment groups. However, more infection-related deaths were observed on belimumab versus placebo, as seen in previous trials. NMSCs and malignancies (excluding NMSC) were similar between treatment groups. Although infrequent, more serious infusion and hypersensitivity reactions were observed with belimumab compared with placebo. The incidence was greater in the belimumab group compared with placebo for the following on-treatment AESI: serious depression/suicide/self-injury, serious depression and serious suicide/self-injury. These observations led to updates to the company Global Data Sheet (core company safety information) and updates to local prescribing information for depression and suicide/self-injury. No suicide-related deaths were reported in the 1-year controlled treatment period (Year 1).

Following Year 1, the BEL115467 study continued to follow participants for a further 4 years (Year 2-5). The objective of the Year 2-5 follow-up period was to assess mortality and new primary malignancy, including NMSC, in adult SLE participants who received either belimumab plus standard therapy or placebo plus standard of care during Year 1 of the study. During the follow-up period, participants did not receive any investigational product as part of the trial and instead received physician-directed standard of care, which could have included commercially-available belimumab by prescription. It should be noted that although the start date of first exposure to commercial Benlysta was collected, no other additional information is available. Treatment group assignment was based on treatment received during the Week 52 double-blind treatment period.

By the end of Year 5 follow-up, the cumulative mortality rate (per 100 participant-years) for the total study population was 0.78 (0.61 in the belimumab group and 0.96 in the placebo group). This is consistent with, and numerically lower than, that expected for the

SLE population based on the reported mortality rate of 1.63 per 100 person-years for an international cohort of 9547 SLE patients that were observed from 1958 to 2001 [Bernatsky, 2006]. The cumulative mortality rate (per 100 participant-years) was numerically lower in the belimumab group as compared with the placebo group by the end of follow-up Years 2-5, which is also consistent with Year 1 data. From a post-hoc summary, 96 participants (2.85%) died in the Year 2-5 follow-up period. By SOC, the highest incidence of deaths during the Year 2-5 follow-up period was due to Infections and infestations (28 total [0.83%]: 14 placebo [0.84%] and 14 belimumab [0.83%]), and Cardiac disorders (17 total [0.51%]: 12 placebo [0.72%] and 5 belimumab [0.29%]). Of the 96 participants (2.85%) who died during follow-up Years 2-5, 58 (3.47%) had received placebo in Year 1. Of the participants who received placebo in Year 1 and died during follow-up Years 2-5, 2 were exposed to commercial Benlysta during the follow-up phase. There was no notable clustering of deaths by PT for either group. Overall, the mortality data suggest that belimumab treatment during Year 1 did not increase risk of all-cause mortality during the follow-up period.

By the end of follow-up Years 2 and 3, the cumulative new primary malignancy participant incidence rate (per 100 participant-years) was numerically lower in the belimumab group compared with the placebo group. By the end of follow-up Years 4 and 5, the rates were similar between the treatment groups. By the end of Year 5 follow-up, the cumulative new primary malignancy participant incidence rate (per 100 participant-years) was 0.39 for the total study population (0.40 in the belimumab group and 0.38 in the placebo group). This is consistent with and numerically lower than the reported malignancy rate of 0.53 per 100 person-years for an international cohort of 16 409 SLE patients who were followed from 1958 to 2009 [Bernatsky, 2013]. The proportion of participants who reported a new primary malignancy for follow-up Years 3 and 4 (0.52% and 0.47%, respectively) was comparable to the proportion during the controlled treatment period in Year 1 (0.47%). The proportion of participants who reported a new primary malignancy in follow-up Years 2 and 5 (0.30% and 0.16%, respectively) was lower than Year 1. Overall, the malignancy data suggest that belimumab treatment during Year 1 did not increase risk for new primary malignancies during the follow-up period. The mortality and new primary malignancy safety data for the Year 2-5 follow-up period did not present new safety concerns for the use of belimumab in patients with active, autoantibody-positive SLE who received standard therapy. The overall safety profile demonstrated in study BEL115467 continues to support a favorable benefit:risk profile of belimumab.

200908 is an open-label, single treatment arm study to evaluate the pharmacokinetics, safety, and pharmacodynamics of SC belimumab plus standard therapy in pediatric participants 5 to 17 years of age, which has completed parts A and B of the study. Part A was the open-label, 12-week treatment phase. Part B was the optional 40 week open-label continuation phase for any participant who completed Part A. Twenty-five pediatric participants were enrolled in the study and all participants completed Part A Twenty -three participants completed Part B. The safety and tolerability profile of 200 mg SC belimumab in pediatric participants observed in this study is consistent with the known safety profile of belimumab. No new safety concerns following treatment with SC belimumab 200 mg were identified in pediatric participants in this study. Overall, the risk/benefit profile of SC belimumab 200 mg in pediatric SLE participants observed in this study is consistent with the known risk/benefit profile of belimumab. There is an optional Access Extension Phase

of the study for eligible participants who completed Part B which is ongoing. Eleven participants enrolled in the ongoing optional Access Extension Phase.

There are a large number of ongoing and completed studies that support the efficacy and safety evaluation of Benlysta IV and SC in the SLE population (see Annex 2). This includes a number of Post Authorization Measure studies adopted in the RMP at the time of the original Benlysta IV approval.

To date, there are 38 ongoing or completed studies of IV and SC belimumab. In addition to SLE and LN, belimumab has been evaluated in a number of other indications including: RA, IMGN, Myasthenia Gravis, Renal Transplant, Sjogren's, Vasculitis, and sequential use with rituximab in adults with SLE. Currently, belimumab is being evaluated for SSc-ILD. A study in subjects with CTD-ILD is also planned.

A tabular listing of all completed and ongoing clinical studies in the pharmacovigilance plan is provided in Annex 2 .

SIII.2 Clinical Trial Exposure

As of 08 March 2024, an estimated 7384 subjects (14 510.8subject years) have been exposed to belimumab and in addition 168 subjects (147.0 subject years) in total have been exposed to belimumab + rituximab, in ongoing and completed GSK-sponsored interventional clinical studies. The cumulative number of subjects from ongoing and completed GSK sponsored clinical studies investigating belimumab for the treatment of SLE and other developmental indications through 08 March 2024 is presented in Table 3.The information for completed clinical studies is sourced from the clinical trial database. For ongoing clinical trials, the cumulative exposure is estimated using the enrolment at the 08 March 2024 DLP and the randomization ratio for the study.

Table 3 Cumulative Number of Subjects from Ongoing and Completed GSK-Sponsored Interventional Studies (08 March 2024)

	Number of Subjects Exposed		
	--		
Study Designs/Treatment	**Ongoing[1]**	**Completed[2]**	**Total[3]**
Healthy Volunteers			
Belimumab	0	287	287
Placebo	0	0	0
Rheumatoid Arthritis Subjects			
Belimumab	0	214	214
Placebo	0	69	69
SLE Subjects			
Intravenous excluding Lupus Nephritis Study (BEL114054)			
Belimumab	142	4595	4693
Placebo	0	3133	3133

	Number of Subjects Exposed		
	--		
Study Designs/Treatment	**Ongoing[1]**	**Completed[2]**	**Total[3]**
Subcutaneous			
Belimumab	9	1084	1093
Placebo	0	280	280
Belimumab+Rituximab co-administration	0	144	144
Total SLE Subjects (excluding LN)			
Belimumab	142	5679	5777
Placebo	0	3413	3413
Belimumab+Rituximab co-administration	0	144	144
Intravenous Lupus Nephritis Study (BEL114054)			
Belimumab	0	347	347
Placebo	0	224	224
Continuation Studies			
SLE Intravenous			
Belimumab	0	609	609
Rheumatoid Arthritis			
Belimumab	0	56	56
IMGN			
Belimumab	0	14	14
Placebo	0	0	0
Myasthenia Gravis			
Belimumab	0	18	18
Placebo	0	22	22
WG/MPA (Vasculitis)			
Belimumab	0	53	53
Placebo	0	52	52
Renal Transplant			
Belimumab	0	12	12
Placebo	0	13	13
Sjogren's Syndrome			
Belimumab	0	24	24
Placebo	0	13	13
Belimumab+Rituximab co-administration	0	24	24
Rituximab	0	25	25
SSc-ILD			
Belimumab	3	0	3
Placebo	2	0	2
Total[3]			
Belimumab	145	7283	7384
Placebo	2	3806	3808

	Number of Subjects Exposed		
	--		
Study Designs/Treatment	**Ongoing[1]**	**Completed[2]**	**Total[3]**
Belimumab+Rituximab co-administration	0	168	168
Rituximab	0	25	25

[1] Ongoing studies: BEL114055 - Part B, 213560, 217091, 218224. Exposure is estimated with enrolment at data lock point and randomization ratio per study.
[2] Completed studies: 200909, BEL114055 - Part A, BEL110751, BEL110752, BEL112232, BEL112233, BEL112234, BEL112341 DB and OL, BEL113750 DB and OL, BEL114333, BEL115467, BEL115471 DB and OL, BEL114243, BEL114424, BEL114448, BEL115123, BEL115466, BEL115470, BEL116119, BEL116472, BEL116027, BEL117100, HGS1006-C1058, LBRA01, LBRA99, LBSL01_M, LBSL01_S, LBSL02, LBSL99, 200339, BEL114674 (terminated with no enrolment), BEL114054 DB and OL, 201842, 209629, 205646, 200908 Parts A & B.
[3] Unique subject counts for Total have been reduced by subjects who participated in another study.

An estimate of cumulative number of subjects exposed to belimumab by age, sex and racial group for completed GSK-sponsored interventional studies with an approved clinical study report (CSR) by 08 March 2024 is presented in Table 4.

Table 4 Cumulative Subject Exposure to Belimumab in Completed GSK-Sponsored Interventional Studies by Age, Sex and Racial group (08 March 2024)

Treatment	Category	Number of Subjects
Belimumab		
	Total [1]	7283
	Age (Years)	
	0 - <5	0
	5 - 17	80
	18 - 64	7023
	65 - 74	155
	>= 75	25
	Sex	
	Male	707
	Female	6576
	Racial Group	
	White	3467
	Asian	1927
	Black	1145
	Other	744
Belimumab+Rituximab co-administration	**Total [1]**	168
	Age (Years)	

Treatment	Category	Number of Subjects
	0 - <5	0
	5 - 17	0
	18 - 64	163
	65 - 74	5
	>= 75	0
	Sex	
	Male	17
	Female	151
	Racial Group	
	White	121
	Asian	18
	Black	23
	Other	6
Total	**Total** [1]	7451
	Age (Years)	
	0 - <5	0
	5 - 17	80
	18 - 64	7186
	65 - 74	160
	>= 75	25
	Sex	
	Male	724
	Female	6727
	Racial Group	
	White	3588
	Asian	1945
	Black	1168
	Other	750

[1] To derive unique subject counts, counts for Total have been reduced by subjects who participated in another study; however all subject exposure has been counted.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5 Exclusion criteria which will remain as contraindications

Criteria	Implications for target population
Hypersensitivity to the active substance or to any of the excipients	Hypersensitivity to the active substance or to any of the excipients is included as a contraindication in the belimumab IV and SC SmPCs.

Table 6 Exclusion criteria which are NOT proposed to remain as contraindications

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Patients with severe active lupus nephritis	Study participation in the belimumab clinical trial program excluded subjects with severe active lupus nephritis as they are at the more severe end of the SLE spectrum and are more likely to require treatment outside of the guidelines of permitted medications.	No	There are no data to support a contraindication in this population. The renal route is not critical to the elimination of monoclonal antibodies like belimumab because their large size prevents efficient filtration through the glomerulus. Because renal elimination is not the major route of belimumab clearance; significant issues associated with treatment of renally impaired patients are unlikely. This is discussed under the Posology and method of administration section and Pharmacokinetic properties section in the IV and SC SmPCs. Study BEL114054 (HGS1006-C1121) assessed the safety and tolerability of

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			belimumab in adult subjects with lupus nephritis. A six-month open label extension has completed.
Patients with severe active central nervous system lupus	Study participation in the belimumab clinical trial program excluded subjects with severe active central nervous system lupus because they were at the more severe end of the SLE spectrum and were more likely to require treatment outside of the guidelines of permitted medications.	Yes	There are no data to support a contraindication in this population. This is discussed under Special warnings and precautions for use in the IV and SC SmPCs.
Patients taking concomitant B-cell targeted therapy or cyclophosphamide	Concomitant B-cell targeted therapy may affect the profile of B-cell response seen with belimumab and could confound the safety or efficacy results. Subjects who received IV cyclophosphamide within 6 months of baseline were excluded because they were likely to be at the more severe end of the SLE spectrum and were therefore more likely to require treatment outside of the guidelines of permitted medications.	Concomitant B-cell targeted therapy: No Cyclophosphamide: No	There are no data to support a contraindication in this population. In the primary safety population, belimumab was not studied in combination with other B cell targeted therapies or intravenous cyclophosphamide. The efficacy and safety of belimumab administered in combination with rituximab to adult subjects with SLE was evaluated in study 205646. The Special Warnings and Precautions for use section of both the IV and SC SmPC were updated to state available data do not support the co-administration of rituximab with Benlysta in patients with SLE. Caution should be exercised if Benlysta is co-administered with

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			other B cell targeted therapy. The safety and efficacy of belimumab was evaluated for the maintenance of remission in subjects with systemic Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) following a standard induction regimen of rituximab or cyclophosphamide. It was also evaluated in BEL114054 in subjects with lupus nephritis in combination with IV cyclophosphamide. The Special warnings and precautions for use section of the SC SmPC was updated to remove reference to cyclophosphamide.
Patients with infections, HIV, or history of or current hepatitis B or C infections	Study participation in the belimumab clinical trial program excluded subjects with long-term recurring infections, HIV, or history of or current hepatitis B or C infections because the mechanism of action of belimumab could increase the potential risk for the development or reactivation of infections.	No	There has been no evidence of reactivation of Hepatitis B or C with belimumab to date. The large safety registry (SABLE) will include evaluation of Hepatitis B and C as part of events of interest. This is discussed under Special warnings and precautions for use in the IV and SC SmPCs. Some belimumab studies may include subjects with a past history of Hepatitis B (HBcAb positive) if HBV DNA is negative at screening.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Patients with hypogammaglobulinemia (defined as IgG <400 mg/dL) or IgA deficiency (defined as IgA <10mg/dL)	Study participation in the belimumab clinical trial program excluded subjects with hypogammaglobulinemia because belimumab may exacerbate pre-existing hypogammaglobulinemia and potentially increase the risk of infection.	No	There is no data to support a contraindication in this population based on the lack of significant changes in IgG or IgA in clinical trials and no indication to date of an increased risk of infection in belimumab subjects with hypogammaglobulinemia. This is discussed under Special warnings and precautions for use in the IV and SC SmPC.
Patients with history of major organ transplant or hematopoietic stem /cell /marrow transplant or renal transplant	Study participation in the belimumab clinical trial program excluded subjects with a history of major organ transplant or hematopoietic stem /cell /marrow transplant or renal transplant. Subjects with a history of transplantation typically have a high foreign antigen load, potential for rejection and are taking immunosuppressant medications. These subjects would likely require treatment outside the guidelines for permitted medications or would have an immune status not typical of SLE subjects, confounding the safety and efficacy results.	No	There are no data that support a contraindication in this population. Belimumab has not been studied in this patient group. This is discussed under Special warnings and precautions for use in the IV and SC SmPC. BEL114424 is a randomized, double-blind, Phase II study in transplant patients to determine if belimumab reduces the occurrence of donor specific antibodies, reducing likelihood of rejection. Overall the data suggest that treatment with belimumab will have a positive impact on antibody mediated graft dysfunction in renal transplantation. The study met the primary efficacy endpoint. Treatment with belimumab 10 mg/kg demonstrated a reduction in naïve B-cells at Week 24 and an increase in memory B-cells (PD

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			endpoint). The safety data review showed no evidence for a new safety signal. Adverse events were consistent with that expected for the population, and consistent with the known safety profile of belimumab. There was no evidence for increased infection risk with the addition of belimumab to standard of care with basiliximab induction, tacrolimus, mycophenolate mofetil and prednisolone maintenance therapy and no apparent imbalances in vital sign, laboratory, or ECG data between the two groups.
Patients with malignant neoplasm within the last 5 years, except for cancers of the skin (basal or squamous cell) that have been completely surgically excised or adequately treated cancer of the uterine cervix	Study participation in the belimumab clinical trial program excluded subjects with malignant neoplasm within the last 5 years, because immunomodulatory medicinal products, including belimumab, may increase the risk of malignancy. Additionally, subjects with a history of malignancy may have a recurrence and may be less likely to complete the trials due to underlying malignancy.	No	There is no data to support a contraindication in this population as this is a theoretical risk. Belimumab has not been studied in this patient group. This is discussed under Special warnings and precautions for use in the IV and SC SmPC. Two studies assess the long-term safety and events of special interest, including malignancy; BEL115467/BASE (long-term post-treatment follow period for years 2 through 5 evaluating mortality and malignancy) has completed. Overall, the malignancy data suggest that belimumab treatment during Year 1 did not

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			increase risk for new primary malignancies during the follow-up period. The new primary malignancy safety data for the Year 2-5 follow-up period presented no new safety concerns for the use of belimumab in patients with active, autoantibody-positive SLE who received standard therapy. BEL116543/SABLE (5-year registry study) is ongoing.
Long-term safety in patients less than 18 years of age	The long-term safety and efficacy of belimumab in children (less than 18 years of age) has not been established. Information required for initial registration was for adults as SLE predominantly occurs in the adult population.	Yes	There is no data to support a contraindication in this population. This is discussed under Posology and Administration in the IV and SC SmPC. PLUTO (BEL114055) is an ongoing long-term safety study of pediatric patients 5 years to 17 years of age who will be followed for safety for up to 10 years after their first IV belimumab dose. The double-blind phase of this trial has completed (Part A). A total of 93 subjects (40 subjects in the placebo group, 53 subjects in the belimumab 10 mg/kg group) received at least 1 dose of study agent during the double-phase. Within the limits of the 1-year data analyzed to date, the benefit:risk profile of IV belimumab 10 mg/kg in pediatric SLE patients appears

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			consistent with that of the adult population. Part B and C of BEL114055 are ongoing, and pediatric patients will be followed for safety for up to 10 years after their first IV belimumab dose.
Lack of information in patients receiving live immunizations	Live vaccines should not be given for 30 days before, or concurrently with belimumab, as clinical safety has not been established. Because of its mechanism of action, belimumab may interfere with the response to immunizations. However, in a small study evaluating the response to a 23-valent pneumococcal vaccine; overall immune responses to the different serotypes were similar in SLE patients receiving belimumab compared with those not receiving belimumab at the time of vaccination.	No	There is no data to support a contraindication in this population as this is a theoretical risk. This is discussed under Special warnings and precautions for use in the IV and SC SmPC.

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	In total, an estimated 7384 subjects (14 510.8 subject years) have been exposed to belimumab and an additional 168 subjects (147.0 subject years) in total have been exposed to belimumab+rituximab coadministration in ongoing and completed clinical studies through 08 March 2024.	Although rare events may not have been observed during belimumab studies, the overall safety profile is as expected based on the mechanism of action of belimumab and remains consistent with the known safety profile of belimumab and/or the population under study. Two studies assess the long-term safety including events of special interest some of which are rare; Completed study BEL115467/BASE (long-term post-treatment follow period years 2 through 5 evaluating mortality and malignancy) and ongoing BEL116543/SABLE (5-year registry study).
Due to prolonged exposure	Exposure in subjects in trials of belimumab administered IV is extensive. Inclusive of data for completed and ongoing IV SLE studies (including LN) through 08 March 2024, 4996 subjects had been treated with belimumab administered IV for at least 6 months at doses of 1 mg/kg, 4 mg/kg, and 10 mg/kg and 3047, 1746, 1344, 1081, 820 and 584 subjects had been treated for ≥1, ≥2, ≥3, ≥4, ≥5 and ≥ 6 years, respectively, with the longest continuous exposure ≥11 years (84 subjects). Long-term (>1.5 years) exposure has been at a 10 mg/kg belimumab dose, providing a relatively large database to evaluate long-term safety of belimumab. Exposure with belimumab SC for completed and ongoing SLE studies through 08 March 2024 is as follows: 830	There were no new safety signals identified with increasing duration of exposure to belimumab. The completed study BEL115467/BASE [long-term post-treatment follow period years 2 through 5 evaluating mortality and malignancy] and ongoing study BEL116543/SABLE will provide additional data on the long-term safety of belimumab.

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
	subjects had been treated for at least 6 months, in most cases at a dose of 200 mg weekly, and 671 and 67 subjects had been treated for ≥1 and ≥2 years, respectively, with the longest continuous exposure ≥3 years (5 subjects).	
Due to cumulative effects	There is a theoretical possibility of cumulative effects with belimumab.	Thus far there is no evidence to suggest cumulative effects for AEs with belimumab.
Which have a long latency	Exposure in subjects in trials of belimumab administered IV is extensive. Inclusive of data for completed and ongoing IV SLE studies (including LN) through 08 March 2024, 4996 subjects had been treated with belimumab administered IV for at least 6 months at doses of 1 mg/kg, 4 mg/kg, and 10 mg/kg and 3047, 1746, 1344, 1081, 820 and 584 subjects had been treated for ≥1, ≥2, ≥3, ≥4, ≥5, and ≥6 years, respectively, with the longest continuous exposure ≥11 years (84 subjects). Long-term (>1.5 years) exposure has been at a 10 mg/kg belimumab dose, providing a relatively large database to evaluate long-term safety of belimumab. Exposure with belimumab SC for completed and ongoing SLE studies through 08 March 2024 is as follows: 830 subjects had been treated for at least 6 months, in most cases at a dose of 200 mg weekly, and 671 and 67 subjects had been treated for ≥1 and ≥2 years, respectively, with the longest	There is currently no evidence to suggest concerns with adverse reactions which have a long latency for belimumab and/or the population under study. Ongoing studies noted above will provide data on the long-term safety and events of special interest, including malignancies.

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
	continuous exposure ≥3 years (5 subjects).	

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table 7 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	There are no adequate and well controlled clinical studies of the use of belimumab in pregnant women. Pregnancy reports received within the GSK Argus Safety Database through 08 March 2024, included 220 from belimumab clinical trials (187 belimumab, and 33 placebo) and 659 from literature, spontaneous reports and PMS studies outside of the non-interventional pregnancy studies (BEL114256/BPR and 213928/bMUM). Additionally, 72 prospective and retrospective belimumab-exposed pregnancy reports were received in the global pregnancy registry (BEL114256/BPR) with an additional 5 lost to follow-up. Due to limitations associated with the BPR, including low enrollment (of the 500 pregnancies that the BPR sought to enroll, only 61 pregnancies were enrolled in the primary [prospective] cohort), it is not possible to draw conclusions about any relationship between belimumab exposure and major birth defects or other pregnancy and infant outcomes of interest. A belimumab pregnancy exposure study (213928/bMUM) in the US and Canada has replaced the global BPR and will evaluate pregnancy outcomes in women with SLE as well as infant outcomes through 1 year. See Section SVII.3.2 for data pertaining to pregnancy reports received to date.
Breastfeeding women	There are no adequate and well controlled clinical studies of the use of belimumab in breastfeeding women. See Section SVII.3.2 for data pertaining to lactation reports received to date.

Type of special population	Exposure
	Cumulatively through 08 March 2024, there were 21 reports of exposure to belimumab during breastfeeding, all of which were spontaneous or post-marketing reports (including BPR reports).
Patients with relevant comorbidities:	
Patients with hepatic impairment:	No formal studies were conducted to examine the effects of hepatic impairment on the pharmacokinetics of belimumab.
Patients with renal impairment	No formal studies were conducted to examine the effects in patients with renal impairment prior to marketing authorization and the exclusion of subjects with severe lupus kidney disease in clinical trials limited the enrolment of subjects with a high degree of renal disease. However, BEL114054 (HGS1006-C1121) assessed the safety and tolerability of belimumab in adult subjects with lupus nephritis Class III, IV or V using the 2003 ISN/RPS criteria. The study met its primary and all major secondary endpoints demonstrating superiority of IV belimumab as compared to standard of care alone in achieving and maintaining renal response and preventing renal flares on the background of clinically meaningful steroid dose reduction. The safety profile was consistent between the treatment groups, and there were no new safety issues identified in the study population as compared to the belimumab safety profile in SLE and the results continue to support the favorable benefit-risk profile of belimumab. The open-label extension is complete.
Patients with cardiovascular impairment	No formal studies were conducted in subjects with cardiovascular impairment.
Immunocompromised patients	No formal studies were conducted in patients with acquired or congenital immunodeficiency syndromes
Patients with a disease severity different from inclusion criteria in clinical trials	Belimumab has not been studied in and is not recommended in patients with severe active central nervous system lupus.

Type of special population	Exposure
Population with relevant different racial and/or ethnic origin	The relatively low number of black patients in both the Phase 2 and 3 studies and the conflicting results made it impossible to draw conclusions about observed treatment differences in the black population. No clear statistical interaction by race was observed, which is consistent with the absence of an identified pathophysiological reason why any race should experience decreased efficacy with belimumab. The double-blind phase of study BEL115471 to evaluate the efficacy and safety of 10 mg/kg belimumab administered IV compared with placebo in adult black subjects with active SLE over a 52-week blinded period has completed. A total of 496 subjects (165 subjects in placebo group; 331 subjects in belimumab 10 mg/kg group) received at least 1 dose of study agent during the double-blind phase of the study. Within BEL115471, the safety profile of IV belimumab 10 mg/kg plus standard therapy was generally comparable with placebo plus standard therapy. In addition, IV belimumab 10 mg/kg plus standard therapy in adult SLE subjects of black race demonstrated an acceptable safety profile consistent with the known safety profile of IV belimumab 10 mg/kg plus standard therapy in adult SLE subjects. No new safety concerns following treatment with IV belimumab 10 mg/kg were identified in subjects of black race. Although not statistically significant for the primary endpoint, the data from BEL115471 have shown a favorable benefit-risk profile of IV belimumab 10 mg/kg as an add-on treatment to standard therapy in black subjects with active, autoantibody positive SLE across a number of clinical measures. Subjects who completed the double-blind phase of BEL115471 were assessed for eligibility to participate in a 6-month extension phase during which they received open-label belimumab 10 mg/kg body weight by IV infusion every 28 days. The open-label extension is completed. The first dose in the extension phase was given at the Day 364/Week 52 visit of the double-blind period, corresponding to Day 1 of the open-label phase after the completion of all Day 364/Week 52 assessments. Subjects participating in the extension phase continued to be monitored for safety and, at a reduced frequency, efficacy. More latitude was permitted for changes in background medication during the extension phase compared with the double-blind phase. No new safety signals were observed in this open-label analysis, and the safety results were consistent with the known safety profile of belimumab 10 mg/kg IV. Overall, no trends of clinical concern were noted with regard to the incidences of AEs, including SAEs and AEs of special interest, over the course of this open-label analysis. The incidences of AEs were generally consistent with that expected in this SLE population. Belimumab 10 mg/kg IV was well tolerated as an add-on therapy to standard of care in the treatment of SLE in subjects of black race.

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other Elderly Children:	No specific geriatric studies were conducted with belimumab for SLE but analyses are ongoing for the pooled data from the elderly (age ≥ 65 years) subpopulation treated in the following: SLE belimumab studies: Pooled: LBSL02 (Phase 2, IV), HGS1006-C1056 (BLISS-76, BEL110751, Phase 3, IV), HGS1006-C1057 (BLISS-52, BEL110752, Phase 3, IV), BEL113750 (NE Asia, IV), HGS1006-C1115 (BLISS-SC, BEL112341, Subcutaneous Phase 3), HGS1006-C1112 (EMBRACE, BEL115471, Black Race, IV), and side-by-side presentation with HGS1006-C1113 (BASE, BEL115467, Safety, IV). Results presented in elderly subjects to date are consistent with what was observed in the broader SLE population. The lack of specific geriatric studies is expected to have little impact since the majority of patients with SLE in the general population are < 65 years of age. An IV and SC Pediatric Investigation Plan has been agreed with the EMA and include assessments of pharmacokinetics, safety and efficacy of IV and SC belimumab in SLE patients aged 5-17 years (inclusive). PLUTO (BEL114055) (Part B and C) is an ongoing study of pediatric patients who will be followed for safety for up to 10 years after their first IV belimumab dose. The double-blind phase of this trial has completed. A total of 93 subjects (40 subjects in the placebo group, 53 subjects in the belimumab 10 mg/kg group) received at least 1 dose of study agent during the double-phase. Within the limits of the 1-year data analyzed to date, the benefit:risk profile of IV belimumab 10 mg/kg in pediatric SLE patients appears consistent with that of the adult population. The IV product SmPC indication in SLE has been extended to include children 5 years of age and older based on the data from the 93 subject BEL114055 study. 200908, an open-label, single treatment arm study to evaluate the pharmacokinetics, safety, and pharmacodynamics of SC belimumab plus standard therapy in pediatric participants 5 to 17 years of age, has completed parts A and B of the study. A population PK analysis of study 200908 and BEL114055 PK data was performed to determine the pediatric SC dose. The dose was chosen to ensure belimumab exposure remains within acceptable limits and is consistent with adult SC exposures in the Phase 3 study BEL112341. PK simulations derived from the population PK model demonstrated that a three-weight band regimen would be appropriate to treat a pediatric population with SLE:

Type of special population	Exposure
Patients of Different Weights:	• 200 mg weekly for patients ≥50 kg • 200 mg every 10 days for patients 30 kg to <50 kg • 200 mg every two weeks for patients 15 kg to <30 kg To assess any potential effect of exposure differences on safety and efficacy, tables were generated for two phase 3 studies, HGS1006-1056 and HGS1006-1057. Safety results for the underweight (BMI <18.5 kg/m2), normal/overweight (18.5 kg/m2 ≤ BMI ≤ 30 kg/ m2) and obese (BMI > 30 kg/ m2) subpopulations were stratified by treatment regimen. Subject numbers were relatively low in the underweight categories and of moderate size in the obese category, while the normal/overweight subjects made up the majority of the phase 3 population. In terms of safety, overall serious and severe AE rates were typically higher for obese subjects. The following analyses focus on whether within obese subjects the increased belimumab exposure due to BMI, especially in the 10 mg/kg group, resulted in pronounced increases in safety event rates compared to placebo. However, no effect of BMI-related exposure differences on incidence rate was apparent. Obese subjects in the10 mg/kg treatment group, the subgroup which would be most affected by increased exposure due to high BMI, had similar or lower rates of overall, serious and severe adverse events compared to the placebo and 1 mg/kg groups. While variations in BMI of belimumab treated subjects are expected to lead to variations in exposure, no safety or efficacy signals where identified for obese and underweight subjects which would warrant dose adjustment beyond the current weight normalized dosing scheme. In SC study BEL112341, when evaluated by weight quartiles AEs and SAEs were generally similar across all quartiles as the study population overall and without meaningful differences between placebo and belimumab. See Other: Children section above for weight based dosing of the SC presentation in pediatric SLE patients.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-authorization exposure

SV.1.1 Method used to calculate exposure

The algorithm used to derive the post-marketing exposure estimate varies per region and by formulation. The US estimate for the IV formulation assumes an average dose per infusion of 760 mg. The estimates from Europe, Emerging Markets and Asia Pacific for the IV formulation assume an average dose per infusion of 700 mg. There are no assumptions regarding compliance, persistence and drop-out rates. The estimate for the SC formulation assumes a standard dose of 200 mg weekly regardless of region. There are no assumptions regarding compliance, persistence and drop-out rates.

SV.1.2 Exposure

Cumulative post-marketing exposure to belimumab is estimated to be 281 758 patient years based on data from IQVIA [previously known as Intercontinental Medical Statistics (IMS) Health] through 31 December 2023. This estimate reflects exposure to both the IV formulation (174 578 patient years) and the SC formulation (107 180 patient years).

A detailed breakdown of cumulative patient exposure data by indication, sex, age, dose, formulation and region for the period 01 July 2011 through 31 December 2023 is presented in Table 8.

Table 8 Exposure table by indication, gender, age group, dose, formulation and region

NUMBER OF PRESCRIPTIONS ('000s) 01 July 2011 to 31 December 2023																		
INDICATION	SEX		AGE GROUP (YEARS)					DOSE				FORMULATION				REGION		
	MALE	FEMALE	UNKNOWN	0-11	12 - 17	18 - 65	65+	UNKNOWN	120MG	400MG	200MG/1ML	UNKNOWN		INTRAVENOUS	Pre-filled Syringe	EU	USA/CANADA	OTHER
SYSTEMIC LUPUS ERYTHEMATOSUS	100	1227	4	1	0	1202	120	8	230	375	455	271		876	455	40	812	479
LUPUS NEPHRITIS	1	15	0	0	0	16	0	0	7	9	0	0		16	0	0	14	2
OTHERS*	5	50	0	0	0	53	1	1	12	8	24	11		31	24	5	38	12

*"Others" include pleural conditions, lupus erythematosus, rheumatoid arthritis, juvenile arthritis, necrotizing vasculopathy, polyarteritis nodosa and related conditions, systemic invasive connective tissue disorder, osteoporosis without pathologic fracture, nephritic syndrome, other diseases of liver.

The data in Table 8 is sourced from IQVIA's "MIDAS Diagnosis Insights (detailed medical data)". The data cover office-based prescribing in over 11 key countries (including major markets in Europe, Asia and the Americas) and it covers patient demographics as well as diagnosis specific prescribing information. Diagnosis Insights data do not include hospital-based doctors, with the exception of Japan, where hospital data is also covered. Medical audits reflect country prescribing practices and care should be taken when comparing

countries or analyzing on a regional or global basis. The data reflect prescriptions that are written. Information regarding prescriptions dispensed and refills are not included.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

A potential for misuse for illegal purposes or abuse has not been identified for belimumab and is considered unlikely from the knowledge of belimumab.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable. This is in line with GPV module V revision 2 which states that the initial identification of safety concerns is expected to be populated with the initial submission of an RMP, either at the time of initial marketing authorization or post-authorization for approved products that previously did not have an RMP.

The initial EU-RMP (version 7) was approved at time of CHMP opinion on 19 May 2011 for the initial Marketing Authorization. This pre-dated this EMA templated section.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The initial EU-RMP included the following list of safety concerns

Identified Risks

Hypersensitivity and Infusion Systemic Reactions
Infections

Potential Risks

Progressive Multifocal Leukoencephalopathy
Malignancies
Immunogenicity
Effects on Immunizations, Including Interactions with Live Vaccines
Psychiatric events including depression and suicidality

Missing information

The initial EU-RMP included the following list of important missing safety information:

Limited data in pregnant and lactating women
Limited data in elderly patients
No data in pediatric patients
Effect of long-term B Cell reduction on safety
Lack of data in SLE patients with severe active lupus nephritis or severe active CNS lupus
Lack of data on effect of stopping treatment (treatment holidays) and on risk of rebound

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Identified Risk: Infections	
Frequency with 95 % CI	OIs are identified using a list of PTs designed to cast a wide net for events potentially indicative of an Opportunistic Infection (OI) in clinical trials and in PM reports. Any identified event is adjudicated by the GSK safety review team (SRT) prior to database release to determine if criteria are met for an OI. Targeted follow-up is sought for events with insufficient information. In general, potential OIs that are non-serious with insufficient information to adjudicate are considered non-opportunistic and potential OI SAEs with insufficient information to adjudicate are considered opportunistic. A list of agreed upon pathogens and infections considered to be opportunistic has been developed for the purpose of adjudication. Where provided below, exposure adjusted event and incidence rates across all SLE (excluding LN) and LN clinical studies of belimumab are estimated from completed studies (i.e. with an authorized CSR by 08 Mar 2024) only. Estimated exposure adjusted event rates of infections that are AESIs as well as fatal infections have been calculated based on SRT adjudicated SAEs in the completed belimumab SLE (excluding LN) and LN studies for comparison with background rates in the SLE and LN populations, respectively. From 09 Mar 2023 to 08 Mar 2024, only 1 SLE study, 200908 Parts A and B completed. No new LN studies have completed since 08 March 2022. Across all completed IV (excluding LN Study BEL114054) and SC SLE studies through 08 March 2024, the total subject-years of belimumab exposure was 12822.9 in 6258 subjects and in the belimumab+rituximab group was 127.3 in 144 subjects. The total subject-years of placebo

Identified Risk: Infections	
	exposure was 3143.9 in 3413 subjects in the placebo group. Based on SRT adjudication of SAEs, in SLE (excluding LN) subjects, there were 23 events of opportunistic infection (excluding herpes zoster and tuberculosis) in 22 belimumab subjects, 0 events in the belimumab+rituximab group and three events of opportunistic infection (excluding herpes zoster and tuberculosis) in 3 subjects in the placebo group. The opportunistic infection (excluding herpes zoster and tuberculosis) event rate in SLE (excluding LN) subjects was 0.18 per 100 subject-years (95% CI: 0.11, 0.27) in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 2.90) in the belimumab+rituximab group, and 0.10 per 100 subject-years (95% CI: 0.02, 0.28) in the placebo group. In SLE (excluding LN) subjects, there were 8 events of opportunistic herpes zoster in 8 belimumab subjects and 0events of opportunistic herpes zoster in any subject in the belimumab+rituximab or placebo groups. The opportunistic herpes zoster event rate in SLE (excluding LN) subjects was 0.06 per 100 subject-years (95% CI: 0.03, 0.12) in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 2.90) in the belimumab+rituximab group, and 0.00 per 100 subject-years (95% CI: 0.00, 0.12) in the placebo group. In SLE (excluding LN) subjects, there were 7 events of opportunistic tuberculosis in 6 belimumab subjects, 0 events in belimumab+rituximab subjects, and 2 events of opportunistic tuberculosis in 2 placebo subjects. The opportunistic tuberculosis event rate in SLE (excluding LN) subjects was 0.05 per 100 subject-years (95% CI: 0.02, 0.11) in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 2.90) in the belimumab+rituximab group, and 0.06 per 100 subject-years (95% CI: 0.01, 0.23) in the placebo group. In the completed IV LN Study BEL114054 through 08 March 2022, the total subject-years of belimumab exposure was 488.0 in 347 subjects. The total subject-years of placebo exposure was 335.6 in 224 subjects in the placebo group.

Identified Risk: Infections	
	Based on SRT adjudication of SAEs, in LN subjects there were 5 events of OI (excluding herpes zoster and TB) in 4 belimumab subjects and 3 events of OI (excluding herpes zoster and TB) in 3 subjects in the placebo group. The OI (excluding herpes zoster and TB) event rate in LN subjects was 1.02 per 100 subject-years (95% CI: 0.33, 2.39) in the belimumab group and 0.89 per 100 subject-years (95% CI: 0.18, 2.61) in the placebo group. In LN subjects there were 4 events of opportunistic herpes zoster in 4 belimumab subjects and no events of opportunistic herpes zoster in any subject in the placebo group. The opportunistic herpes zoster event rate in LN subjects was 0.82 per 100 subject-years (95% CI: 0.22, 2.10) in the belimumab group and 0.00 per 100 subject-years (95% CI: 0.00, 1.10) in the placebo group. In LN subjects there was 1 event of opportunistic TB in 1 belimumab subject and 1 event of opportunistic TB in 1 placebo subject. The opportunistic TB event rate in LN subjects was 0.20 per 100 subject-years (95% CI: 0.01, 1.14) in the belimumab group and 0.30 per 100 subject-years (95% CI: 0.01, 1.66) in the placebo group. The rate of OIs to date among belimumab-treated subjects is less than the range reported in the literature for patients with SLE (1.3 to 1.9 per 100 patient-years [Zonana-Nacach, 2001; Gladman, 2002; Fernández-Nebro, 2012]). When considered against regions where TB is endemic, these rates are also less than those reported in SLE patients: a rate of 0.15 per 100 patient-years has been reported for lupus patients in Turkey, and a rate as high as 2.45 per 100 patient-years has been reported in SLE patients in India [Erdozain, 2006]. Across all completed studies for all indications through 08 March 2024, the total subject-years of belimumab exposure was 14101.9 in 7283 subjects and in the belimumab+rituximab group was 147.0 in 168 subjects. The total subject-years of placebo exposure was 3616.9 in 3806 subjects in the placebo group. Based on the SRT adjudication of SAEs, for all indications, there were 67 deaths in the belimumab group, 1 death in the belimumab+rituximab group and 35

Identified Risk: Infections	
	deaths in the placebo group. The mortality incidence rate in all indications was 0.48 per 100 subject-years (95% CI: 0.37, 0.60) in the belimumab group, 0.68 per 100 subject-years (95% CI: 0.02, 3.79) in the belimumab+rituximab group, and 0.97 per 100 subject-years (95% CI: 0.67, 1.35) in the placebo group. Based on the SRT adjudication, of SAEs, for all indications, there were 37 deaths due to infection in subjects in the belimumab group, 0 deaths due to infection in the belimumab+rituximab group, and 12 deaths due to infection in subjects in the placebo group. The mortality due to infection incidence rate in all indications was 0.26 per 100 subject-years (95% CI:0.18, 0.36) in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 2.51) in the belimumab+rituximab group, and 0.33 per 100 subject-years (95% CI: 0.17, 0.58) in the placebo group. The belimumab mortality due to infection incidence rate of 0.26 per 100 subject-years (95% CI: 0.18,0.36) is consistent with the rate reported in the literature for SLE patients (0.17-1.66 per 100 patient-years) [Terrier, 2010; Cervera, 2003; Cervera__R, 2009; Cervera_R2006; Mok, 2003; Fernández, 2012; Alarcón, 2001] Across all completed IV (excluding LN Study BEL114054) and SC SLE studies through 08 March 2024, the total subject-years of belimumab exposure was 12822.9 in 6258 subjects and in the belimumab+rituximab group was 127.3 in 144 subjects. The total subject-years of placebo exposure was 3143.9 in 3413 subjects in the placebo group. Across all completed IV (excluding LN) and SC SLE studies of belimumab, through 08 March 2024, there were 57 deaths in the belimumab group, no deaths in the belimumab+rituximab group, and 29 deaths in the placebo group. The mortality incidence rate in SLE (excluding LN) subjects was 0.44 per 100 subject-years (95% CI: 0.34, 0.58) in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 2.90) in the belimumab+rituximab group, and 0.92 per 100 subject-years (95% CI: 0.62, 1.32) in the placebo group.

Identified Risk: Infections	
	The mortality incidence rate in the belimumab group is less than that reported in the literature for SLE (1.63 per 100 patient-years; 95% CI: 1.54, 1.72) [Bernatsky, 2006], although the historical rate may be an overestimate for the current mortality rate given the decreases in SLE mortality rates seen over time. For all completed IV (excluding LN) and SC SLE studies of belimumab, there were 33 deaths due to infection in subjects in the belimumab group, no deaths due to infection in the belimumab+rituximab group, and 9 deaths due to infections in subjects in the placebo group. The mortality due to infection incidence rate in SLE (excluding LN) subjects was 0.26 per 100 subject-years (95% CI: 0.18, 0.36) in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 2.90) in the belimumab+rituximab group, and 0.29 per 100 subject-years (95% CI: (0.13, 0.54) in the placebo group. In SLE (excluding LN) subjects there were 14 events of fatal pneumonia in 14 subjects in the belimumab group, 0 events of fatal pneumonia in the belimumab+rituximab group, and 2 events of fatal pneumonia in 2 subjects the placebo group. The event rate of fatal pneumonia in SLE (excluding LN) was 0.11 per 100 subject-years (95% CI: 0.06, 0.18) in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 2.90) in the belimumab+rituximab group, and 0.06 per 100 subject-years (95% CI: 0.01, 0.23) in the placebo group. In the completed IV belimumab study BEL114054 in LN, through 8 March 2022, there were 5 deaths in the belimumab group, and 3 deaths in the placebo group. The mortality incidence rate in LN subjects was 1.02 per 100 subject-years (95% CI: 0.33, 2.39) in the belimumab group and 0.89 per 100 subject-years (95% CI: 0.18, 2.61) in the placebo group. In the completed IV belimumab study BEL114054 in LN, there were 2 deaths due to infection in subjects in the belimumab group and 2 deaths due to infection in subjects in the placebo group. The mortality due to infection incidence rate in LN subjects was 0.41 per 100 subject-years (95% CI: 0.05, 1.48) in the belimumab group and 0.60 per 100 subject-years (95% CI: 0.07, 2.15) in the placebo group.

Identified Risk: Infections	
	In LN subjects there were 2 events of fatal pneumonia in 2 belimumab subjects and 1 event of fatal pneumonia in 1 placebo subjects**.** The fatal pneumonia event rate in LN subjects was 0.41 per 100 subject-years (95% CI: 0.05, 1.48) in the belimumab group and 0.30 per 100 subject-years (95% CI: 0.01, 1.66) in the placebo group. Language in the current product information indicates some infections are severe or fatal (see Preventability section below). Deaths due to infection will continue to be monitored through normal proactive pharmacovigilance in the clinical development program and spontaneous reporting. * The SRT for belimumab provides a forum for the proactive, aggregate and holistic evaluation of the safety profile of belimumab over the developmental lifecycle of the medicine by GSK members from Clinical, Statistics, Safety and Epidemiology.
Seriousness/outcomes	The incidence rate for belimumab infectious deaths in SLE (excluding LN) subjects by 8th March 2024 (0.26 per 100 subject years; 95% CI: 0.18, 0.36) remains within the range reported in the literature for patients with SLE (0.17-1.66 per 100 patient-years) [Alarcón 2001; Cervera, 2003; Cervera, 2006; Cervera, 2009; Mok, 2003; Terrier, 2010]). There is not enough data to establish a causal association with belimumab and infection -related deaths and GSK will continue to closely monitor this aspect of the risk. <u>Infections of Special Interest in the Primary Safety Population:</u> Infections of special interest were evaluated in the SLE IV controlled repeat dose (CRD) studies (primary safety population: LBSL02, HGS1006-C1056, HGS1006-C1057) and included cellulitis (and similar events such as erysipelas, impetigo and abscess), fungal infections, herpes viral infections, sepsis, respiratory infections (URTIs, LRTIs) and pneumonia, and possible OIs. In general, rates of these categories of infections were comparable across treatment groups. There was a slightly higher incidence of lower respiratory infections in the belimumab groups (8.6%, 11.3% and 12.0% in the placebo, 1 mg/kg and 10 mg/kg groups, respectively).

Identified Risk: Infections	
	Pneumonia was reported in similar proportions of subjects across all treatment groups. See below for discussion of OIs. Because gastroenteritis viral was reported for greater proportions of subjects in belimumab groups compared with placebo in Study C1056 (1.5%, 4.4%, and 4.4% in the placebo, 1 mg/kg, and 10 mg/kg treatment groups, respectively), a post-hoc exploratory analysis was performed using a composite definition for gastrointestinal infections. This composite analysis demonstrated that gastrointestinal infections were reported for 8.6%, 11.3% and 10.7% of subjects in the placebo, 1 mg/kg and 10 mg/kg treatment groups, respectively. The higher incidence of these infections in the belimumab groups was mainly driven by gastroenteritis and viral gastroenteritis events (i.e., gastroenteritis viral¸ gastrointestinal viral infection, viral diarrhea). The number of serious gastrointestinal infections was low (4 events in the placebo group, six in the 1 mg/kg group, and 4 in the 10 mg/kg group). <u>Sepsis:</u> Sepsis and serious infections are not unexpected in SLE patients and occur more commonly than in the non-SLE population. In published, randomized controlled trials of SLE subjects, the sepsis rate ranged from 0.59 (treated) to 2.27 (placebo) per 100 subject-years [Merrill, 2010b]. In prospective SLE studies, the incidence rates of sepsis ranged from 0.26 to 6.56 per 100 patient-years [Cervera, 2003; Gladman, 2002; Bosch, 2006; Fernández-Nebro, 2012]. Sepsis and sepsis related events up to 08 March 2013 were evaluated across belimumab SLE clinical trials. The estimated rate of sepsis for the belimumab group was 35/6535.9 subject-years (0.54 per 100 subject-years, 95% CI: 0.37, 0.74). Comparison with the background rates of sepsis reported for SLE patients in the literature (above) as well as comparison with the rate observed for the placebo group in belimumab SLE clinical trials (4/767.5 subject-years or 0.52 per 100 subject-years, 95%CI: 0.14, 1.33) does not indicate an increased risk of sepsis in belimumab-treated subjects. <u>Infections Associated with Immunosuppressant Use:</u>

Identified Risk: Infections	
	The incidence of infection AEs in the SLE IV CRD studies (primary safety population) was evaluated based on baseline immunosuppressant usage. Though the incidence rates for infection, as well as related, serious and severe infections were slightly higher across placebo and belimumab treatment groups for subjects who were taking immunosuppressants at baseline compared with those who were not, there was no apparent belimumab treatment effect or dose relationship. Specifically, for MMF, the rate of serious infections was higher across groups for subjects taking MMF, but there was no apparent belimumab treatment effect or dose relationship. <u>Infections Associated with Lymphopenia, Neutropenia, Immunoglobulin or T-cell Abnormalities (IV):</u> Infectious AEs in the SLE IV CRD studies (primary safety population) were summarized by worst Grade (Grade 3 or 4) lymphopenia, neutropenia, T-cell level and immunoglobulin level (IgG, IgM, and IgA) toxicity experienced. The results of these analyses must be interpreted with caution due to the potential multi-factorial impact of disease activity, baseline laboratory parameters and treatment. In addition, a temporal relationship between the onset of an infection and laboratory measures could not be examined due to the lack of laboratory data available at specific, relevant time points. In addition, too few subjects experienced Grade 3 or 4 neutropenia, Grade 3 or 4 IgG toxicity, low IgM levels, low IgA levels or low T cell levels to draw conclusions. Belimumab subjects who experienced Grade 3 or 4 lymphopenia had a slightly higher incidence of overall infection AEs than subjects who did not have Grades 3 or 4 lymphopenia (63%, 75%, 76% versus 68%, 70%, 68% in the placebo, 1 mg/kg and 10 mg/kg treatment groups, respectively). Additionally, serious infection AEs were experienced by a greater number of belimumab subjects with Grades 3 or 4 lymphopenia compared with those without Grades 3 or 4 lymphopenia (3%, 9%, 7% versus 6%, 6%, 5% in the placebo, 1 mg/kg and 10 mg/kg treatment groups, respectively). A higher proportion of belimumab-treated subjects with Grade 3 or 4 lymphopenia reported respiratory infections (52% and 60% in the 1 mg/kg and 10 mg/kg treatment groups, respectively, compared with those without Grades 3 or 4

Identified Risk: Infections	
	lymphopenia, (51% and 49%, respectively); for placebo-treated subjects, the reverse trend was observed (42% subjects with Grade 3 or 4 lymphopenia vs. 51% of subjects without). The trend of an increased incidence in belimumab-treated subjects with Grade 3 or 4 lymphopenia experiencing infectious AEs of pneumonia was also noted. Finally, both possible OIs (disseminated CMV and acinetobacter bacteremia, see OIs) reported in the SLE IV CRD studies (primary safety population) were in subjects who had Grade 3 or 4 lymphopenia at some time during the study, though not temporally related to the onset of the OIs. It is important to note, however, that the number of subjects who developed Grade 3 or 4 lymphopenia was similar across placebo and belimumab-treated groups. <u>Combined IV (all doses) and SC Studies</u> In the pooled analysis of the IV and SC intent-to-treat population (LBSL02, HGS1006-C1056, HGS1006-C1057, BEL112341, BEL113750, BEL115471), the rate of infections and infestations (all events) was higher in belimumab (63.8%) compared to placebo (61.6%); however, the rate of serious infections and infestations (all events) was slightly lower in belimumab (5.4%) compared to placebo (5.9%). In the analysis of the pooled intent-to-treat population, all adjudicated OIs were reported in 157/2815 (5.6%) in the combined IV and SC belimumab group which was lower than 92/1355 (6.8%) in the placebo group. Serious OIs were similar across the belimumab [25/2815 (0.9%)] and placebo [14/1355 (1.0%)] groups. Active tuberculosis was reported in 4/2815 (0.1%) in the combined IV and SC belimumab group and 5/1355 (0.4%) in the placebo group. Serious active tuberculosis was reported in 3/2815 (0.1%) in the combined IV and SC belimumab group and 3/1355 (0.2%) in the placebo group. All adjudicated herpes zoster was reported in 106/2815 (3.8%) in the combined IV and SC belimumab group and 59/1355 (4.4%) in the placebo group. Serious herpes zoster was reported in 15/2815 (0.5%) in the combined IV and SC belimumab group and 5/1355 (0.4%) in the placebo group.

Identified Risk: Infections	
	Sepsis was reported in 20/2815 (0.7%) in the combined IV and SC belimumab group and 10/1355 (0.7%) in the placebo group. Serious sepsis was reported in 18/2815 (0.6%) in the combined IV and SC belimumab group and 6/1355 (0.4%) in the placebo group. <u>Long-Term IV Belimumab Data</u> The long-term data for infections provided below is from the combined IV SLE trials (final data) and represents GSK adjudicated infection events. The rate of infections is reported per 100 subject years. Rates of all adjudicated serious OIs at any time post-baseline is 0.2 with the highest incidence in years 0-1, 1-2 and 3-4 (0.2, 0.2 and 0.2, respectfully). Rates of serious OIs excluding TB and herpes zoster any time post baseline is 0.1. This rate was similar across individual time periods with no events reported in years 5+. Rates of opportunistic active TB any time post baseline is <0.1 with no events in any years except years 5-6 (0.2). There were no serious opportunistic active TB events. Rates of serious opportunistic herpes zoster any time post baseline is <0.1 with no serious events reported after years 0-1. The most commonly reported infections in all intervals were upper respiratory tract infection, nasopharyngitis, UTI and influenza. Serious infections included pneumonia, cellulitis, pneumonia bacterial, gastroenteritis viral, and UTI. After 2 years of treatment, the rate of serious infections in each interval was less than the range of serious infections reported in the literature for patients with SLE: 2.64 (95% CI: 1.95, 3.51) to 12.65 (95% CI: 8.34 – 18.40) per 100 patient-years [Fernández-Nebro, 2012; Gladman, 2002; Merrill, 2010a; Terrier, 2010; Zonana-Nacach, 2001; Lertchaisataporn, 2013]. <u>Hepatitis:</u> Patients with SLE do not appear to be at increased risk for Hepatitis B or C infections compared with the risks in

Identified Risk: Infections	
	the general population [AbuShakra, 1997; Berkun, 2009; Zhao, 2010]. However, treatment with rituximab is associated with reactivation of hepatitis B infections, primarily in oncology populations, though reactivation of HBV following treatment with rituximab also has been observed in the rheumatology population [Lovric, 2009]. There has been no evidence of reactivation of hepatitis B or C with belimumab to date; however, subjects with current of past hepatitis B or C infections were excluded from trials. In addition, there were no reported cases of hepatitis B or C reported in the large safety study (BEL115467/BASE). The large safety registry (SABLE) will include evaluation of Hepatitis B and C as events of interest. BEL115471 Two subjects died during the double-blind phase of the study (0 placebo and 2 belimumab [0.6%]). Both deaths in the belimumab group were infectious events (meningitis and pneumonia). Although there was a numerical imbalance in the incidence of deaths due to infection in the belimumab group in this study, the infection-related deaths had confounding factors, and both were considered not related to belimumab by the investigator. The rate of opportunistic infection AESI, including active TB and herpes zoster, was lower in the belimumab 10 mg/kg group (0.6%) compared to the placebo group (1.2%). There was one case of recurrent herpes zoster infection in the belimumab group and two cases of disseminated herpes zoster in the placebo group. PML – see PML risk below. BEL116027 In this study of 80 patients, reported infections and infestations were higher in the long-term discontinuation (LTD) group, 59.0%, and the treatment-holiday (TH) re-start phase, 63.9%, compared to the treatment control (TC), 48.3% and TH-holiday phase, 33.3%. One subject in the LTD group had an adverse event of special interest (AESI) of non-serious, recurrent Herpes Zoster. One subject in the LTD group had an AESI of sepsis that was considered serious. There were no deaths related to infections reported in any group or phase of the study. There was no clear increase in the proportion of subjects with AE of infection with belimumab treatment and

Identified Risk: Infections	
	reported infections were consistent with those previously observed in other belimumab studies. BEL115467 In this study of 4,003 subjects with SLE (1:1 randomization), the overall incidence of all infections of special interest was lower in the belimumab 10 mg/kg group (1.8%) compared with placebo (2.5%) during the on-treatment period. With the exception of serious sepsis which was reported for 0.5% of belimumab subjects compared with 0.3% of placebo subjects, the incidence of all categories of infection AESI in the belimumab group was lower than or equal to placebo group. No subjects in either treatment group had a serious opportunistic, serious recurrent, or serious disseminated herpes zoster infection per GSK adjudication. One (<0.1%) subject in the belimumab 10 mg/kg group with no prior history of CNS lupus developed neurologic deficits and was diagnosed with PML during the on-treatment period of the study. The SAE was moderate in intensity and considered to be possibly related to study agent by the investigator. The duration of the event was 450 days and the event recovered/resolved with sequelae. The incidence of infection AESI that led to premature discontinuation of study agent during the on-treatment period was 0.6% for both treatment groups. During the on-study period, the overall incidence of all infections of special interest was lower in the belimumab 10 mg/kg group (1.9%) compared with placebo (2.9%). The incidence was higher in the belimumab group compared with placebo for the following infection AESI: serious adjudicated opportunistic infections (<0.1% placebo, 0.3% belimumab), adjudicated opportunistic infections excluding tuberculosis and herpes zoster (placebo <0.1%, belimumab 0.3%), serious adjudicated opportunistic infections excluding tuberculosis and herpes zoster (<0.1% placebo, 0.2% belimumab) and serious sepsis (0.5% placebo, 0.6% belimumab). There was a higher incidence of fatal infections in the belimumab 10 mg/kg group compared with placebo. This finding is consistent with observations of previously completed belimumab studies [Furie, 2011; Navarra, 2011].

Identified Risk: Infections	
	Infection-related deaths during the on-treatment period were reported in 3/2001 (0.15%) subjects in the placebo group and 9/2002 (0.45%) subjects in the belimumab group. Infection-related deaths during the on-study period were reported in 8/2001 (0.40%) subjects in the placebo group and 12/2002 (0.60%) subjects in the belimumab group. Overall, the majority of belimumab deaths were infection-related with the majority of placebo deaths being due to varying causes, including vascular, gastrointestinal, respiratory, SLE-related or unknown. However, serious infections, opportunistic infections and other infections of interest did not occur more frequently in the belimumab group. <u>BEL114055</u> Overall, evidence from BEL114055 suggests that the AESIs are consistent for adults and children. In BEL114055 (PLUTO), the System Organ Classes of adverse events with a notable difference (≥10% difference) between treatment groups were infections and infestations (70.0% placebo, 56.6% belimumab) musculoskeletal and connective tissue disorders (32.5% placebo, 20.8% belimumab), renal and urinary disorders (17.5% placebo, 7.5% belimumab), and metabolism and nutrition disorders (10.0% placebo, 0 belimumab). The SOC with the highest incidence of drug-related AEs overall was infections and infestations (22.5% placebo, 11.3% belimumab). When considered by SOC, severe AEs infections and infestations were observed in the placebo (5.0%) and belimumab (5.7%) groups. The incidence of serious adverse events (SAEs) in the infections and infestations SOC was 12.5% for placebo and 7.5% for belimumab. When compared with the pooled subcutaneous/intravenous datasets submitted in the SC submission (data lock 19August 2015), representing data reported for up to 52 weeks of treatment with belimumab, the overall incidence of AEs in the Infections and Infestations SOC for adults (66.7%) was slightly higher compared with 56.6% of belimumab-treated pediatric subjects. When belimumab-treated adults and pediatric subjects are compared for incidence of serious infection, the rate is slightly higher for pediatric subjects (7.5%) compared with adults (5.3%). There was one death due

Identified Risk: Infections	
	to infection in a belimumab-treated subject, which occurred during the open-label phase of the study as described below. The frequency of infections of special interest was also higher in the belimumab-treated pediatric subjects (13.2%) compared with adults (4.7%). However, it is important to acknowledge the limitations of this comparison (e.g., single small pediatric trial versus pooled data from the much larger studies in adults). Importantly, for the pediatric study, the incidence of infections of special interest (13/100 patient-years) compares favorably with the background incidence of infections in children with SLE per Hiraki et al (i.e., serious infection. defined as hospitalization) at 10.42/100 patient-years [Hiraki, 2017]. Safety data collection is ongoing in the open label extension phase of BEL1140555 (Part B) which continues in children with SLE for up to 10 years after their first belimumab dose. Part B has been ongoing since 2013 with no new safety findings identified to date. <u>BEL114054</u> This phase 3 study evaluated the efficacy and safety of belimumab plus standard of care versus placebo plus standard of care in 448 adult subjects with active lupus nephritis. The double blind and open label phases have completed. In the 104 week double-blind phase, the highest incidence of SAEs overall occurred in infections and infestations SOC (17.0% placebo, 13.8% belimumab), with serious infections reported in the cyclophosphamide (CYC)/ azathioprine (AZA) subgroup (5.1% placebo, 16.7% belimumab) and mycophenolate mofetil (MMF) subgroup (21.1% placebo, 12.8% belimumab). There was no clustering of events. Importantly, 4 out of 10 belimumab subjects with serious infections experienced the events within first 2 weeks of randomization and after only 1 dose of belimumab. Overall, serious infections in the first 24 weeks were reported in 8.9% placebo, and 8.5% belimumab subjects likely due to increased immunosuppression and corticosteroid use. After Week 24, serious infections were reported in 9.2% placebo subjects and 6.1% belimumab

Identified Risk: Infections	
	subjects. This trend was also seen in the CYC/AZA and MMF subgroups. Infections of special interest included: opportunistic infections (OI), herpes zoster (HZ), tuberculosis (TB) 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 were observed during the first 24 weeks of treatment in both treatment arms (2.2% placebo and 3.1% belimumab), which was likely due to intensive immunosuppression and high doses of corticosteroids. This observation decreased during the post-24 week period of the study (1.0% placebo and 1.0% belimumab). 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 24 weeks (5.6% placebo, 4.1% belimumab). Events of serious HZ occurred in a small number of subjects (2 placebo, 5 belimumab). The serious events (belimumab group) occurred evenly between the induction subgroups: 2 subjects (CYC/AZA) and 3 subjects (MMF) and between study phases: 3 subjects (baseline to Week 24) and 2 subjects (post Week 24). Opportunistic HZ (per GSK adjudication) occurred in 3 subjects receiving placebo and 9 subjects receiving belimumab. A higher proportion of these cases were in the MMF subgroup (1 placebo, 7 belimumab) primarily driven by 5 events of recurrent HZ in the belimumab subjects. Of the subjects with opportunistic zoster (belimumab group) 3 were serious and 3 developed disseminated HZ (MMF subgroup). The higher proportion of belimumab subjects with opportunistic or serious herpes zoster was observed during the first 24 weeks of treatment in both groups compared to post-24 weeks, likely due to the increased risk of HZ infection in LN patients with renal flare while receiving intensive immunosuppression and high doses of corticosteroids.

Identified Risk: Infections	
	There were no clinically meaningful imbalances identified in the incidence of infections of special interest between treatment groups. AEs resulting in IP discontinuation were the same between the treatment groups. Infections were the most common AEs leading to IP discontinuation in the overall population. Deaths (n=11) were balanced between treatment groups, both on- and off-treatment, and were mainly due to infections. In the 28 week open label extension, there were 255 patients evaluable for safety (123 patients received placebo during the double blind phase and 132 patients received belimumab during the double blind phase). Belimumab 10 mg/kg IV was well tolerated as an add-on to standard therapy in the treatment of subjects with LN. The incidences of AEs were generally consistent with that expected in this LN population. One subject in the placebo to belimumab 10 mg/kg IV group died during the open-label phase of the study due to multiple organ dysfunction syndrome, sepsis secondary to healthcare-associated pneumonia, and chronic kidney disease. The most frequent AEs reported in ≥5% of subjects in either treatment group during the open-label phase were upper respiratory tract infection, urinary tract infection, arthralgia, and nasopharyngitis. A total of 15 (5.9%) subjects experienced at least one SAE during the open-label phase. The highest incidence of SAEs overall occurred in the infections and infestations SOC (4.3%); there were no trends in the types of infections reported and the numbers were small. The SOC with the highest incidence of AEs related to investigational product (IP) overall was infections and infestations (13.3% overall, 13.8% placebo to belimumab 10 mg/kg IV group, 12.9% belimumab 10 mg/kg IV group). The incidence of AEs related to IP overall for all other SOCs was low (≤3.1%). The PT with the highest incidence of AEs related to IP overall was upper respiratory tract infection (3.9% overall, 4.9% placebo to belimumab 10 mg/kg IV group, 3.0% belimumab 10 mg/kg IV group). No severe AEs occurred in ≥5% of subjects overall in any SOC. When considered by SOC, the SOC with the highest incidence overall was the SOC of infections and infestations (2.7% overall).

Identified Risk: Infections	
	When considered by PT, the highest incidence of severe AEs overall was pneumonia (0.8%). Adverse events leading to IP discontinuation were most commonly reported in the PT of cellulitis (0.8% [n=2 subjects] overall, 0 in the placebo to belimumab 10 mg/kg IV group, 1.5% [n=2 subjects] in the belimumab 10 mg/kg IV group). Infections of special interest included: all OI, HZ, TB and sepsis. Overall, serious infections of special interest were observed in 2 subjects (0.8%) (0 placebo to belimumab 10 mg/kg IV group, 2 subjects [1.5%] belimumab 10 mg/kg IV group). The AE PTs were disseminated TB and HZ. Both AEs were serious adjudicated OI. All serious infections of special interest occurred in the MMF subgroup. The incidence of HZ events overall during the open-label phase was 2.0% (n=5 subjects) (1.6% [n=2 subjects] placebo to belimumab 10 mg/kg IV group, 2.3% [n=3 subjects] belimumab◦10 mg/kg IV group). All HZ events occurred in the MMF subgroup (2.1% placebo to belimumab 10 mg/kg IV group, 2.9% belimumab 10 mg/kg IV group). The incidence of opportunistic and serious HZ events overall during the open-label phase was 0.4% (n=1 subject) (0 placebo to belimumab 10 mg/kg IV group, 0.8% [n=1 subject] belimumab 10 mg/kg IV group) for each special interest category. Overall, no trends were noted with regards to the incidences of AEs, including SAEs and AEs of special interest. No new safety signals were observed in the open-label phase. The safety results were consistent with the known safety profile of belimumab 10 mg/kg IV. Though GSK have insufficient data to conclude a causal relationship between belimumab and opportunistic or fatal infection at this time, the sponsor strengthened the infection warning and precaution in the reference safety information (RSI), stating, *"In controlled clinical studies, fatal infections were uncommon, but occurred more frequently in patients receiving belimumab compared with placebo. Overall, the incidence of serious infections was similar across the belimumab and placebo groups."*

Identified Risk: Infections	
Severity and nature of risk	The majority of infectious AEs were mild to moderate in intensity. In the combined IV and SC CRD studies (pooled IV: C1056/C1057/LBSL02 + BEL112341-SC; Intent-to-Treat population), the overall rate of severe and life-threatening infections occurred in 2.7% in belimumab and placebo groups.
Background incidence/prevalence	The range of serious (i.e., requiring hospitalization and antimicrobial therapy) infections reported in the literature for patients with SLE is 2.64 (95% CI: 1.95, 3.51) to 12.65 (95% CI: 8.34, 18.40) per 100 subject years [Fernández-Nebro, 2012; Gladman, 2002; Terrier, 2010; Zonana-Nacach, 2001; Lertchaisataporn, 2013]. The rate of OIs reported in the literature for patients with SLE is 1.3 to 1.9 per 100 patient-years [Zonana-Nacach, 2001; Gladman, 2002; Fernández-Nebro, 2012]. The range of TB infections reported in the literature for patients with SLE living in countries where TB is endemic is 0.15 per 100 patient-years for patients in Turkey and 2.45 per 100 patient-years for patients in India [Erdozain, 2006]. The death rate from infections reported in the literature for patients with SLE is 0.17-1.66 per 100 patient-years [Terrier, 2010; Cervera, 2003; Cervera, 2009; Cervera, 2006; Mok, 2003; Fernández-Nebro, 2012; Alarcón 2001].
Risk groups or risk factors	Infections are common sources of morbidity and mortality in patients with autoimmune diseases such as SLE. In addition to common and chronic infections, OIs including TB are also known to occur in patients with autoimmune diseases. The primary risk factor for infections, in addition to the disease itself, is the use of immunosuppressive agents, notably steroids and cytotoxic agents (e.g., cyclophosphamide, azathioprine, and MMF).
Potential mechanisms	The SLE population is at risk for infection due to their underlying disease and SoC medications. To date, there is no definitive evidence that belimumab increases the rate of infection. However, theoretically, belimumab may increase the risk of infection due to its mechanism of action of inhibiting BLyS with subsequent effects on B cells.

Identified Risk: Infections	
Preventability	The IV and SC SmPCs includes wording in Section 4.4 (Special Warnings and Precautions for Use) applicable to both pediatric and adult patients and states that the mechanism of action of belimumab could increase the development of infections, including opportunistic infections. In controlled clinical studies, the incidence of serious infections was similar across the belimumab and placebo groups; however, fatal infections (e.g., pneumonia and sepsis) occurred more frequently in patients receiving belimumab compared with placebo. Recommendations are provided to the HCP in SmPC Section 4.4.. The risk of using belimumab in patients with active or latent tuberculosis is unknown. The PIL also includes instruction for patients to inform their doctors if they have a current or long-term infection or if they often get infections. Additional wording in Section 4.8 indicates that risk of infection may be more likely in the pediatric patients 5 to 11 years of age. Pediatric adverse event data for infection by age subset is presented in 4.8. The SLE population is at risk for infection due to their underlying disease and standard medications; prophylaxis and/or treatment as indicated per SoC are commonly used to decrease morbidity and mortality due to infectious complications.
Impact on individual patient	OI can be a major cause of morbidity and mortality in immunocompromised patients. These infections usually require treatment and if serious, may require hospitalization. Infections can cause a loss of work or personal time and an increased monetary burden. The MAH is conducting a prospective observational registry (SABLE) in patients receiving commercial belimumab to further evaluate the safety of IV and SC belimumab in the SLE population by assessment of the incidence of serious and OIs.
Potential public health impact of safety concern	None
Evidence source	Data are referenced in the Clinical Summary of Safety (see Module 2.7.4 sequence 0135)
MedDRA terms	Infections and Infestations SOC

Identified Risk: Psychiatric Events Including Depression and Suicidality	
Frequency with 95 % CI	Depression events were identified using the PTs from the depression (excluding suicide and self-injury) SMQ plus additional terms added by the sponsor. Suicidality were identified using the Suicide/Self-Injury SMQ (plus additional terms added by the sponsor). Where provided below, event rates across all SLE (excluding LN) and LN clinical studies of belimumab are estimated from completed studies (i.e. with an authorized CSR by 08 Mar 2024) only and are based on SRT adjudication of SAEs. From 09 Mar 2023 to 08 Mar 2024, only 1 SLE study, 200908 Parts A and B completed. No new LN studies have completed since 08 March 2022. Estimated rates of suicidality have been calculated in the belimumab SLE studies for comparison with background rates in the SLE population. Estimated event rates of suicidality have been calculated for the IV belimumab LN Study 114054 also. Across all completed IV (excluding LN Study BEL114054) and SC SLE studies through 08 March 2024, the total subject-years of belimumab exposure was 12822.9 in 6258 subjects and in the belimumab+rituximab group was 127.3 in 144 subjects. The total subject-years of placebo exposure was 3143.9 in 3413 subjects in the placebo group. Based on SRT adjudication of SAEs, in SLE (excluding LN) subjects there were 17 events of suicidal ideation which occurred in 17 belimumab subjects, 0 events in belimumab+rituximab subjects and 7 events of suicidal ideation in 7 placebo subjects. The suicidal ideation event rate in SLE (excluding LN) subjects was 132.58 per 100,000 subject-years (95% CI: 77.23,212.27) in the belimumab group, 0.00 per 100 000 subjects-years (95% CI: 0.00,2898.37) in the belimumab+rituximab group and 222.65 per 100 000 subject-years (95% CI: 89.52,458.75) in the placebo group. Based on SRT adjudication of SAEs, in SLE (excluding LN) subjects there were 22 events of serious suicidal behavior (non-fatal suicide attempts and completed suicide) in 22 belimumab subjects, 1 event in 1 belimumab-rituximab subject, and 5 events of suicidal behavior in 5 placebo subjects. The suicidal behavior event rate in SLE (excluding LN) subjects was 171.57 per

Identified Risk: Psychiatric Events Including Depression and Suicidality	
	100 000 subject-years (95% CI: 107.52,259.76) in the belimumab group, 785.70 per 100 000 subject-years (95% CI: (19.89,4377.66) in the belimumab-rituximab group, and 159.04 per 100 000 subject-years (95% CI: 51.64,371.14) in the placebo group. Based on SRT adjudication of SAEs, in SLE (excluding LN) subjects there were 4 subjects in the belimumab group and 0 subjects in the belimumab+rituximab group or the placebo group who completed suicide. The completed suicide event rate in SLE (excluding LN subjects) was 31.19 per 100 000-subject-years (95% CI: 8.50,79.87) in the belimumab group, 0.00 per 100 000 subject-years (95% CI: 0.00,2898.37) in the belimimab+rituximab group and 0.00 per 100,000 subject-years (95% CI: 0.00,117.34) in the placebo group. Based on SRT adjudication of SAEs, in SLE (excluding LN) subjects there were 39 events of total suicidality (suicidal behavior/ completed + suicidal ideation) which occurred in 39 belimumab subjects, 1 event in 1 belimumab-rituximab subject, and 12 events of total suicidality in 12 placebo subjects. The total suicidality event rate in SLE (excluding LN subjects) was 304.14 per 100 000 subject-years (95% CI: 216.28,415.77) in the belimumab group, 785.70 per 100 000 subject-years (95% CI 19.89,4377.66) in the belimumab-rituximab group, and 381.69 per 100 000 subject-years (95% CI: 197.23,666.74) in the placebo group. Based on SRT adjudication of SAEs, in SLE (excluding LN) subjects there was 1 event of serious self-injurious behavior without suicidal intent in 1 subject in the belimumab group, no events of serious self-injurious behavior without suicidal intent in the belimumab+rituximab group, and 1 such event that occurred in 1 subject in the placebo group. The self-injurious behavior without suicidal intent event rate in SLE (excluding LN) subjects was 7.80 per 100 000 subject-years (95% CI: 0.20,43.45) in the belimumab group, 0.00 per 100 000 subject-years (95% CI: 0.00,2898.37) in the belimumab+rituximab group, and 31.81 per 100 000 subject-years (95% CI: 0.81,177.22) in the placebo group.

Identified Risk: Psychiatric Events Including Depression and Suicidality	
	Estimated event rates of suicidality have been calculated based on SRT adjudicated SAEs in the completed belimumab IV Study BEL114054 in LN. Across all completed LN IV studies (BEL114054) through 08 March 2022, the total subject-years of belimumab exposure was 488.0 in 347 subjects in the belimumab group. The total subject-years of placebo exposure was 335.6 in 224 subjects in the placebo group. In LN subjects there were no events of serious suicidal ideation in any belimumab or placebo subject. The suicidal ideation event rate in LN subjects was 0.00 per 100,000 subject-years (95% CI: 0.00, 755.96) in the belimumab group and 0.00 per 100,000 subject-years (95% CI: 0.00, 1099.1) in the placebo group. There were 2 events of serious suicidal behavior (non-fatal suicide attempts and completed suicide) in 2 belimumab subjects and no event in any placebo subject in completed LN IV studies. The suicidal behavior event rate in LN subjects was 409.86 per 100,000 subject-years (95% CI: 49.64, 1480.6) in the belimumab group and 0.00 per 100,000 subject-years (95% CI: 0.00,1099.1) in the placebo group. There were no subjects in the belimumab group and no subjects in the placebo group who completed suicide in completed LN IV studies. The completed suicide event rate in LN subjects was 0.00 per 100,000- subject-years (95% CI: 0.00, 755.96) in the belimumab group and 0.00 per 100,000 subject-years (95% CI: 0.00, 1099.1) in the placebo group. There were 2 events of total suicidality (suicidal behavior/ completed + suicidal ideation) which occurred in 2 belimumab subjects and 0 events of total suicidality in 0 placebo subjects in completed LN IV studies. The total suicidality event rate in LN subjects was 409.86 per 100,000 subject-years (95% CI: 49.64, 1480.6) in the belimumab group and 0.00 per 100,000 subject-years (95% CI: 0.00, 1099.1) in the placebo group. In LN subjects there was no self-injurious behavior without suicidal intent in the belimumab or placebo group. The self-injurious behavior without suicidal intent event rate in

Identified Risk: Psychiatric Events Including Depression and Suicidality	
	LN subjects was 0.00 per 100,000 subject-years (95% CI: 0.00, 755.96) in the belimumab group and 0.00 per 100,000 subject-years (95% CI: 0.00, 1099.1) in the placebo group. The belimumab estimates are consistent with the background rates for completed suicide (10.0 to 2181.8 per 100,000 patient-years) [Cervera, 2003; Li-Yu, 2007] and for suicide or suicide attempts (117 per 100,000 patient years; 95% CI: 46.9, 240) reported for SLE patients in observational studies or retrospective chart reviews [Karassa, 2003].
Seriousness/outcomes	<u>IV (all doses) and SC pooled data</u> In the pooled analysis of SLE subjects (intent-to-treat population) in belimumab controlled-repeat dose (CRD) studies (BEL110751, BEL110752, LBSL02, BEL112341, BEL113750, BEL115471): Serious suicide/self-injury: There were 4/1355 (0.3%) in the placebo group and 4/2815 (0.1%) in the combined IV/SC belimumab group. Deaths: There were 6/1355 (0.4%) deaths in the placebo group and 16/2815 (0.6%) deaths in the combined IV/SC belimumab group. <u>C-CASA retrospective analysis (Initial Benlysta IV BLA/MAA):</u> SAE narratives from all belimumab SLE trials (C1057, C1056, LBSL02, C1066, C1074, LBSL99 and C1070 were analyzed by a subject matter expert clinician at Columbia University. Additionally, verbatim terms for all AEs were searched for words that could be associated with suicidality, as described in [Posner, 2007]; no additional events were identified. The more severe, conservative code was selected in cases when more than one code could apply with the exception of one event that could have coded as either “suicide attempt” or “other” but was changed to “other” after it was discovered that the event occurred prior to the subject’s participation in the study. In the primary safety population, there were three events of completed or attempted suicide: one completed suicide in each of the belimumab treatment groups and one attempted suicide in the placebo group. There were three

Identified Risk: Psychiatric Events Including Depression and Suicidality	
	cases of suicidal ideation, two in the 1 mg/kg belimumab group and one in the 4 mg/kg group. All other SAEs were coded as not associated with suicidal behavior. In the uncontrolled, long-term studies in which all subjects received belimumab and that included approximately 2,400 subject-years exposure from almost 1,400 patients, there was one completed suicide, four attempted suicides and two cases of suicidal ideation. The analysis found no difference from placebo in the primary safety population with regard to suicidal behaviors (completed suicide and suicide attempt), though ascertainment bias is possible given the retrospective nature of the review. The rate of suicide/suicide attempt reported in the primary safety population for belimumab (0.13 per 100 subject-years) was similar to the rate reported for placebo patients (0.14 per 100 subject-years). Moreover, these estimates are consistent with the background rates for completed suicide (0.02 to 2.18 per 100 patient-years) [Cervera, 2003; Li-Yu, 2007] and for suicide or suicide attempts (0.12 per 100 patient-years, 95% CI: 0.05, 0.24) [Karassa, 2003] reported for SLE patients in observational studies or retrospective chart reviews. <u>Columbia –Suicide Severity Rating Scale</u> In the BEL112341 (SC) study, suicidality assessments were completed at every visit using the C-SSRS. Two subjects (0.7%) in the placebo group and 7 (1.3%) in the belimumab 200 mg SC group had C-SSRS suicidal ideation at any time during treatment (double-blind phase), regardless of whether the subject had a history of pre-treatment suicidal ideation or behavior. No subjects had suicidal behavior at any time during treatment according to C-SSRS assessments. Of the 14 subjects in the placebo group who had a history of pre-treatment suicidal ideation or behavior, 12 had no on-treatment ideation or behavior; 32 of the 36 subjects in the belimumab 200 mg SC group who had a history of pre-treatment suicidal ideation or behavior had no on-treatment ideation or behavior. Three (0.5%) subjects in the belimumab group who had no C-SSRS history of pre-treatment suicidal ideation or behavior shifted to having on-treatment suicidal ideation (i.e., had treatment-emergent suicidal ideation); no subject shifted to treatment-emergent suicidal behavior. None of these three subjects had more severe suicidal ideation per the C SSRS. One of the three subjects had a “yes” response to C-SSRS item 3 (ideation without intent to act);

Identified Risk: Psychiatric Events Including Depression and Suicidality	
	none of these three subjects had a "yes" response to item 4 (ideation with some intent to act, without a specific plan). A suicide/self-injury AESI was reported for two of the three subjects (non-serious suicidal ideation per SMQ search; serious, suicidal ideation per SMQ search and sponsor adjudication), and one subject had no suicidal-type AEs. <u>Pre-registration IV studies</u> The IV belimumab studies showed an increased incidence in neuropsychiatric disorders for belimumab compared with placebo, mainly driven by reports of depression. This difference could not be explained by imbalances in medication at baseline since the proportions of subjects receiving concomitant medications for depression and suicide/self-injury were similar across treatment groups. However, in the 10 mg/kg group in the Phase 3, IV SLE studies, a slightly greater proportion of subjects reported a medical history of depression and suicide/self-injury at baseline, which could indicate a slightly greater predisposition for the development or worsening of depression than in the other treatment groups. A retrospective C-CASA analysis suggested there was no difference between belimumab and placebo with regard to suicidal behaviors in the primary safety population and, across all SLE studies, a rate of suicidal behaviors during treatment with belimumab that is consistent with the rate reported in the literature for patients with SLE. <u>SC studies</u> The SC study showed an increased incidence in neuropsychiatric disorders in placebo compared to belimumab, mainly driven by reports of insomnia. Depression was also higher in placebo compared to belimumab, but suicidal ideation was reported higher in belimumab compared to placebo. This is supported by the C-SSRS data used in the BEL112341 study that reported suicidal ideation as higher any time during treatment (double-blind phase) in belimumab regardless of whether the subject had a history of pre-treatment suicidal ideation or behavior. No subjects reported suicidal behavior at any time during treatment according to C-SSRS assessments. <u>Long-Term IV Belimumab Data</u> The information provided below is from the combined IV SLE trials (final data) and represents GSK adjudicated psychiatric events.

Identified Risk: Psychiatric Events Including Depression and Suicidality	
	Serious suicide/self-injury: the anytime post baseline rate was 0.1 per 100 subject years with the highest incidences in years 2-3 (0.3) and 4-5 (0.4) with no events after year 7. Serious suicidal behavior: the anytime post baseline incidence was 11/7236 (0.2 per 100 subject years) with the highest rates in years 2-3 and 4-5 (both with a rate of 0.4 per 100 subject years) with no events after year 7. Serious completed suicides: the anytime post baseline incidence was <0.1 per 100 subject years, with similar rates reported in years 2-3 (<0.1 per 100 subject years) and 3-4 (0.1 per 100 subject years) and no events occurring after year 4. Serious suicide ideations: the anytime post baseline rate was <0.1 per 100 subject years with no events in years 0-5 and 6-11+. One event (0.2 per 100 subject years) occurred in years 5-6. <u>BEL115471</u> In this study, the incidence of suicide/self-injury AESI per SMQ was 1.2% in the placebo group and 0.6% in the belimumab group. Suicidal ideation, per GSK adjudication, was reported in 2 subjects in the placebo group (1.2%) and no subject in the belimumab 10 mg/kg group. No cases of suicidal behavior or completed suicides occurred. <u>BEL115467</u> In this study of 4,003 subjects with SLE (1:1 randomization), serious adverse events (SAE) of suicidal ideation of behavior or self-injury (GSK adjudicated) were reported in 0.7% (n=15) of subjects receiving belimumab intravenously 10mg/kg (IV) vs. 0.2% (n=5) of subjects taking placebo. SAEs of depression (CMQ) were reported in 0.3% (n=7) of subjects receiving belimumab 10mg/kg IV vs. <0.1% (n=1) taking placebo. On the Columbia-Suicide Severity Rating Scale (C-SSRS), 2.4% (n=48) subjects on belimumab 10mg/kg IV reported suicidal ideation or behavior and 2.0% (n=39) subjects on placebo reported suicidal ideation or behavior. In study BEL115467, the incidence was greater in the belimumab group compared with placebo for the following on-treatment AESI: serious depression/suicide/self-injury, serious depression and serious suicide/self-injury. These observations led to recent updates to the company Global Data Sheet (core

Identified Risk: Psychiatric Events Including Depression and Suicidality	
	company safety information) and updates to local prescribing information for depression and suicide/self-injury. No suicide-related deaths were reported in study BEL115467. * One patient on belimumab in the BASE study (BEL115467) reported a suicide attempt on the Columbia Suicide Severity Rating Scale (C-SSRS) with a corresponding SAE of 'exacerbation of depression'. In the BASE CSR the subject was not included as having suicidal behavior (per GSK adjudication) as the SAE narrative, on which the adjudication was based, did not report suicidality. The subject was however included in a CSR summary of suicidality combining SAE adjudicated outcome and C-SSRS data. <u>BEL116027</u> In this study of 80 patients, one subject in the long-term discontinuation group had an AESI of depression, and one subject in the treatment control group had an AESI of poor-quality sleep. No cases of suicidal behavior or completed suicides occurred. <u>BEL114054</u> In this Phase 3 study of 448 adult subjects with active lupus nephritis, events of depression/suicide/self-injury occurred more commonly in the placebo group (7.1% placebo, 4.9% belimumab). There was one SAE of suicidal behavior (attempted suicide) in the belimumab group in a subject with a history of manic-depression who had recently self-discontinued prescribed antidepressant. The subject recovered and completed belimumab treatment throughout the open label extension. The open label extension has completed. In the open label extension, there were 255 patients evaluable for safety (123 patients received placebo during the double blind phase and 132 patients received belimumab during the double blind phase). Overall, events of depression/suicide/self-injury occurred in 6 subjects (2.4%) (2 subjects [1.6%] placebo to belimumab 10 mg/kg IV group, 4 subjects [3.0%] belimumab 10 mg/kg IV group). There was one SAE of suicidal behavior; this SAE was in a subject in the CYC/AZA subgroup in the belimumab 10 mg/kg IV group. The subject was diagnosed with an adjustment disorder, recovered, and

Identified Risk: Psychiatric Events Including Depression and Suicidality	
	completed belimumab treatment throughout the open-label phase. <u>Summary:</u> Neuropsychiatric events are well recognised in the SLE population, with a wide range of prevalence of depression or mood disorders, due in part to variability in assessment methods used across studies, [Bachen, 2009; Hanly, 2007], and with a prevalence that is substantially higher than the general population. Patients with SLE are at 4 to 10-fold greater risk for suicide than the general population reference for 4-fold greater risk [Harris,1994]; and 10-fold risk [Jarpa, 2011].
Severity and nature of risk	The majority of psychiatric AEs in the primary safety population were mild to moderate in intensity. Severe AEs occurred in 0.4% in the belimumab group in the combined IV and SC CRD studies (pooled IV: C1056/C1057/LBSL02 + BEL112341-SC; Intent-to-Treat population) and in 0.3% in the placebo group studies. There were 2 completed suicides in belimumab groups in these studies. A retrospective C-CASA analysis across belimumab IV SLE studies C1056, C1057 and LBSL02 (primary safety population) suggested there was no difference between belimumab and placebo with regard to suicidal behaviors. In BEL115467, severe psychiatric AEs occurred in 0.5% (10/2002) of subjects receiving belimumab as compared to 0.1% (3/2001) in placebo. There were no completed suicides in Year 1 of this study.
Background incidence/prevalence	Neuropsychiatric events are well recognized in the SLE population, with a wide range of prevalence of depression or mood disorders, due in part to variability in assessment methods used across studies, [Bachen, 2009; Hanly, 2007], and with a prevalence that is substantially higher than the general population. Patients with SLE are at 4-to 10-fold greater risk for suicide than the general population reference for 4-fold risk: [Harris,1994], and 10-fold risk [Jarpa, 2011]. The background rate for Incident depression (self-report, psychiatrist diagnosis or treatment with psychotherapy or antidepressant medication) in SLE is 2.97 per 100 patient-years (95% CI: 2.64, 3.34). [Huang, 2014] Karassa et al [Karassa, 2003] describe a retrospective assessment of suicide and suicide attempt in the first 300 patients with SLE attending a lupus clinic over a

Identified Risk: Psychiatric Events Including Depression and Suicidality	
	20-year period. Using the conservative assumption that all patients had 20 years of follow-up, the rate of suicide and suicide attempt would be 0.12 (95% CI 0.05, 0.24) per 100 patient-years.
Risk groups or risk factors	Unknown
Potential mechanisms	The SLE population is at risk for depression and suicidal behavior due to their underlying chronic disease. There is no known pharmacologic basis for an association between belimumab, or any other monoclonal antibody, and psychiatric events.
Preventability	Physicians should assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with Benlysta and continue to monitor patients during treatment. Physicians should advise patients (and caregivers where appropriate) to contact their health care provider about new or worsening psychiatric symptoms. In patients who experience such symptoms, treatment discontinuation should be considered. The risk and benefit of continued treatment with Benlysta should be assessed for patients who develop such symptoms.
Impact on individual patient	Depression and suicidal ideation/behavior can amplify physical symptoms; impair daily functioning, increased adverse health behaviors decrease self-care and increased mortality.
Potential public health impact of safety concern	None
Evidence source	Imbalance seen in initial Benlysta IV pre-registration trials and then imbalance seen in BEL115467 post approval study.
MedDRA terms	Depression CMQ and Suicide/Self-Injury SMQ

Potential Risk: Progressive Multifocal Leukoencephalopathy (PML)	
Frequency with 95% CI	Cumulatively through 08 March 2024, across all clinical trials and spontaneous reports, 14 cases medically confirmed with a coded event PT, PML were received. Of these 14 cases, 11 cases of PML with a confirmed diagnosis have been received. All 11 cases (10 spontaneous and 1 clinical trial) are confounded by the underlying disease (SLE), concurrent medical conditions,

	and/or concomitant corticosteroid and/or other immunosuppressant medications. See information under Identified Risk: Infections on PML event reported in BEL115467 (BASE study). Cumulative incidence rates of PML are presented from completed IV and SC studies of belimumab, excluding LN and also rates for IV belimumab in LN Study 114054. From 09 Mar 2023 to 08 Mar 2024, only 1 SLE study, 200908 Parts A and B completed. No new LN studies have completed since 08 March 2022. Across all completed IV (excluding LN Study BEL114054) and SC SLE studies through 08 March 2024, the total subject-years of belimumab exposure was 12822.9 in 6258 subjects and in the belimumab+rituximab group was 127.3 in 144 subjects. The total subject-years of placebo exposure was 3143.9 in 3413 subjects in the placebo group. Based on SRT adjudication of SAEs, in SLE (excluding LN) subjects there was 1 event of PML in the belimumab group and no events of PML in the belimumab+rituximab or placebo groups. The PML event rate in SLE (excluding LN) subjects was 7.80 per 100 000 subject-years (95% CI: 0.20,43.45) in the belimumab group, 0.00 per 100 000 subject-years (95% CI: 0.00,2898.37) in the belimumab+rituximab group, and 0.00 per 100 000 subject-years (95% CI: 0.00,117.34) in the placebo group. Across all completed LN IV studies (114054) through 08 March 2022, the total subject-years of belimumab exposure was 488.0 in 347 subjects in the belimumab group. The total subject-years of placebo exposure was 335.6 in 224 subjects in the placebo group. In LN subjects (Study BEL114054) there were no events of PML in the belimumab or placebo groups. The PML event rate in LN subjects was 0.00 per 100,000 subject-years **(**95% CI: 0.00, 755.96) in the belimumab group and 0.00 per 100,000 subject-years (95% CI: 0.00, 1099.1) in the placebo group. A causal association between belimumab and PML has not been established and appropriate Warning and Precaution language is included in the current product

	labeling. GSK will continue to monitor and report on cases of PML as an AE of special interest.
Seriousness/outcomes	PML can be a fatal disease and substantial neurological deficits generally remain permanent in surviving patients. As of 08 March 2024, 1 total cases medically confirmed with a coded event PT of PML were received. Of these 14 cases, 11 cases of PML with a confirmed diagnosis have been received. All 11 cases are confounded by the underlying disease (SLE), concurrent medical conditions, and/or concomitant corticosteroid and/or other immunosuppressant medications.
Severity and nature of risk	PML has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including with belimumab treatment for SLE. PML may confer additional risk among SLE patients. The outcome of PML is often fatal in the vast majority of patients afflicted and this prognosis has been observed among SLE patients [Amend, 2010; Carson, 2009].
Background incidence/prevalence	The rate of PML reported in the literature for SLE patients ranges from 1.0 per 100,000 patient-years (95% CI: 0.03, 5.5) to 2.4 per 100,000 patient-years (95% CI: 0.1, 13.2) [Foskett, 2009; Amend, 2010]. Although the incidence of PML in the general population is not known due to limited published data, substantial information points toward an increased risk for PML in SLE compared to both the general population and rheumatic diseases [Amend, 2010, Arkema, 2012, Molloy, 2009; Molloy, 2012; Molloy, 2008; Nived, 2008]. These findings suggest that the risk of PML in patients with rheumatic diseases, especially SLE, is not wholly attributable to the intensity of iatrogenic immunosuppression [Molloy, 2012; Molloy, 2008].
Risk groups or risk factors	Infections, including PML, are common sources of morbidity and mortality in patients with autoimmune diseases such as SLE. The primary risk factor for infections, in addition to the disease itself, is the use of immunosuppressive agents, notably steroids and cytotoxic agents (e.g., cyclophosphamide, azathioprine, and MMF).
Potential mechanisms	The SLE population is at risk for infection, including PML, due to their underlying disease and SoC medications. To date, there is no definitive evidence that belimumab increases the rate of PML. However, theoretically, belimumab may increase the risk of infection, including PML, due to its mechanism of action of inhibiting BLyS with subsequent effects on B cells.

Preventability	The IV and SC SmPCs includes wording in Section 4.4 (Special Warnings and Precautions for Use) noting PML has been reported with belimumab treatment for SLE and patients should be monitored for PML. Recommendations for HCPs on what to do if PML is suspected are provided in SmPC Section 4.4. The SLE population is at risk for infection, including PML, due to their underlying disease and standard medications; prophylaxis and/or treatment as indicated per SoC are commonly used to decrease morbidity and mortality due to infectious complications. The MAH is conducting a prospective observational registry (SABLE) in patients receiving commercial belimumab to further evaluate the safety of belimumab in the SLE population by assessment of the incidence of serious and OIs, including PML.
Impact on individual patient	PML is a rare disease that can be fatal and substantial neurological deficits generally remain permanent in surviving patients. It causes inflammation of the white matter of the brain causing impairment of the transmission of nerve impulses. Surviving patients are generally left with substantial neurological deficits.
Potential public health impact of safety concern	None
Evidence source	Data are referenced in the Clinical Summary of Safety (see Module 2.7.4 sequence 0135)
MedDRA terms	Infections and Infestations SOC, adjudicated by GSK SRT

Potential Risk: Malignancies	
Frequency with 95% CI	Malignant neoplasms are identified using sub-SMQs of Malignant or unspecified tumours (20000091) and Malignancy related conditions (20000092) based on PT as prescribed by the SMQ. The sub-SMQ of Malignant or unspecified tumours contains two further subcategories: "Malignant Tumours" and "Tumours" of unspecified malignancy." Tumours of unspecified malignancy are reviewed by GSK and identified as malignant or non-malignant for reporting. Where provided below, event rates are estimated from completed IV (excluding LN Study BEL114054) and SC

Potential Risk: Malignancies	
	SLE studies and LN studies through 08 March 2024. Estimated event rates of malignancies have been calculated based on SRT adjudicated SAEs in the completed belimumab SLE (excluding LN) studies for comparison with background rates in the SLE population. Cumulative incidence rates of malignancies are presented from completed IV and SC studies of belimumab, excluding LN and also rates for IV belimumab in LN Study 114054. From 09 Mar 2023 to 08 Mar 2024, only 1 SLE study, 200908 Parts A and B completed. No new LN studies have completed since 08 March 2022. Across all completed IV (excluding LN Study BEL114054) and SC SLE studies through 08 March 2024, the total subject-years of belimumab exposure was 12822.9 in 6258 subjects and in the belimumab+rituximab group was 127.3 in 144 subjects. The total subject-years of placebo exposure was 3143.9 in 3413 subjects in the placebo group. Based on SRT adjudication of SAEs, in SLE (excluding LN) subjects there were 49 events of malignant neoplasms (excluding non-melanoma skin cancer [NMSC]) in 49 belimumab subjects, 0 events of malignant neoplasms (excluding NMSC) in 0 belimumab+rituximab subjects, and 8 events of malignant neoplasms (excluding NMSC) in 8 placebo subjects. The malignant neoplasms **(**excluding NMSC) event rate in SLE (excluding LN subjects) was 0.38 per 100 subject years (95% CI: 0.28, 0. 51) in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 2.90) in the belimumab+rituximab group and 0.25 per 100 subject years (95% CI: 0.11, 0.50) in the placebo group. Across all completed IV LN studies (BEL114054) through 08 March 2022, the total subject-years of belimumab exposure was 488.0 in 347 subjects in the belimumab group. The total subject-years of placebo exposure was 335.6 in 224 subjects in the placebo group. Based on SRT adjudication of SAEs, in LN subjects there were 2 events of malignant neoplasms (excluding NMSC) in 2 belimumab subjects, and 0 events of malignant neoplasms (excluding NMSC) in 0 placebo subjects. The malignant neoplasms (excluding NMSC) event rate in LN subjects was 0.41 per 100 subject-years (95% CI: 0.05,

Potential Risk: Malignancies	
	1.48**)** in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 1.10) in the placebo group. These rates are consistent with the rate of malignant neoplasms, excluding NMSC, observed in the SLE international cohort (0.53 per 100 subject years, 95% CI: 0.48, 0.59); incidence ratio 0.87 (0.59, 1.29) [Bernatsky, 2005]. Although the clinical trial rate for overall malignancy is higher for belimumab compared with placebo, this result is biased by differential duration of on treatment follow up for belimumab treated subjects when compared with placebo treated subjects. This reflects both short open label extension periods of double blind trials in addition to long term open label extension trials in the clinical program. Placebo treated subjects generally have data collected for a total duration of 1 year, whereas belimumab treated subjects may have reporting on such events for as long as 10+ years, given on treatment follow up and data collection in the Long-Term Extension trials. Though calculating event rates based on subject years of exposure helps control for bias during the same risk period, this method becomes less effective when time at risk between cohorts vary, which is of particular interest given the latency characteristics of malignancies. It is therefore helpful, when study data include long-term uncontrolled data, to include comparisons with population rates reported in the literature, *as is reported above*. In our Long Term Extension trials (BEL112233-C1066, BEL112234-C1074, and BEL112626-LBSL99), when considered by-year intervals in which an event occurred, the rate of malignancy revealed no trends of clinical concern, with lack of observed rising rates of malignancy over time overall or for any category. Additionally, malignancies were evaluated during the post-treatment follow up period of BEL115467 (BASE), a large safety study, which included follow-up of all subjects (active and placebo) who gave consent to be contacted yearly for 5 years to assess malignancy status. After year 1, subjects in BASE were no longer on study therapy. By the end of follow-up Years 2 and 3, the cumulative new primary malignancy participant incidence rate (per 100 participant-years) was numerically lower in the belimumab group compared with the placebo group. By the end of follow-up Years 4 and 5, the rates were similar between the treatment groups. By the end of Year 5 follow-up, the cumulative new primary malignancy participant incidence

Potential Risk: Malignancies	
	rate (per 100 participant-years) was 0.39 for the total study population (0.40 in the belimumab group and 0.38 in the placebo group). This is consistent with and numerically lower than the reported malignancy rate of 0.53 per 100 person-years for an international cohort of 16 409 SLE patients who were followed from 1958 to 2009 [Bernatsky, 2013]. Overall, the data suggest that belimumab treatment during Year 1 did not increase risk for new primary malignancies during the follow-up period. In addition, malignancies will be evaluated as a primary objective in the 5-year prospective observational registry (SABLE, BEL116543). Across all completed IV (excluding LN) and SC SLE studies through 08 March 2024, based on SRT adjudication of SAEs, there were 6 events of B-cell lymphoma which occurred in 6 subjects in the belimumab group and no events of B-cell lymphoma in the belimumab +rituximab or placebo groups. The B-cell lymphoma event rate in SLE (excluding LN) subjects was 0.05 per 100 subject-years (95% CI: 0.02, 0.10) in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 2.90) in the belimumab+rituximab group and 0.00 per 100 subject years (95% CI: 0.00, 0.12) in the placebo group. The B-cell lymphoma event rate in SLE (excluding LN) subjects was 0.05 per 100 subject-years (95% CI: 0.02, 0.10) in the belimumab group which is consistent with the rate of B cell lymphoma observed in an international SLE cohort (0.061 per 100 patient-years, 95% CI: 0.045, 0.081) [Bernatsky, 2005]. In the completed IV LN Study BEL114054 through 08 March 2022, based on SRT adjudication of SAEs, there were no events of B-cell lymphoma which occurred in the belimumab group and no events of B-cell lymphoma in the placebo group. The B-cell lymphoma event rate in LN subjects was 0.00 per 100 subject-years (95% CI: 0.00, 0.76) in the belimumab group and 0.00 per 100 subject-years (95% CI: 0.00, 1.10) in the placebo group. Across all IV (excluding LN Study BEL114054) and SC SLE clinical trials through 08 March 2024, based on SRT

Potential Risk: Malignancies	
	adjudication of SAEs, there were 14 events of NMSC which occurred in 14 subjects in the belimumab group, 0 events in the belimumab+rituximab group and 1 event of NMSC in 1 subject in the placebo group. The NMSC event rate in SLE (excluding LN) subjects was 0.11 per 100 subject-years (95% CI: 0.06, 0.18) in the belimumab group, 0.00 per 100 subject-years (95% CI: 0.00, 2.90) in the belimumab+rituximab group and 0.03 per 100 subject-years (95% CI: 0.00, 0.18) in the placebo group. In completed IV LN Study BEL114054 through 08 March 2022, based on SRT adjudication of SAEs, there were no events of NMSC in the belimumab group and no event of NMSC in the placebo group. The NMSC event rate in LN subjects was 0.00 per 100 subject-years (95% CI: 0.00, 0.76) in the belimumab group and 0.00 per 100 subject-years (95% CI: 0.00, 1.10) in the placebo group. Malignancy (including NMSC) will be evaluated in the five-year observational safety registry (SABLE).
Seriousness/outcomes	<u>IV (all doses) and SC pooled analysis</u> In the pooled analysis of SLE subjects (intent-to-treat population) in belimumab controlled-repeat dose (CRD) studies (BEL110751, BEL110752, LBSL02, BEL112341, BEL113750, BEL115471), GSK adjudicated malignancy events are listed below: Malignancies excluding NMSC: There were 2/1355 (0.1%) in the placebo group and 8/2815 (0.3%) in the combined IV/SC belimumab group. NMSC: There were 1/1355 (<0.1%) in the placebo group and 4/2815 (0.1%) in the combined IV/SC belimumab group. <u>Long-Term IV Belimumab Data</u> The information provided below is from the combined IV SLE trials (final data) and represents malignancy events. In the combined IV analysis, the incidence of all malignancies at any time post baseline, excluding NMSC, was 36/7236 subject years (0.5 per 100 subject years)

Potential Risk: Malignancies	
	with the lowest rate at years 0-1 (<0.1 per 100 subjects) and highest at years 9-10 (2.8 per 100 subjects). In HGS1006-C1066/BEL112233, the long-term continuation study of HGS1006-C1056, the overall rate of malignant neoplasms excluding NMSC was low (0.7 events per 100 subject years). When considered by year intervals in which an event occurred, the rate of malignant neoplasms excluding NMSC ranged from 0.4/100 subject years during Year 1-2 to 1.9/100 subject years during Year 6-7 and was 0/100 subject years in Year 0-1, Year 4-5, and Year 5-6. No trends were observed for malignant neoplasm rates over time for any category. In LBSL99/BEL112626, the long-term continuation study of LBSL02, the overall rate of malignant neoplasms excluding NMSC was 0.8 events per 100 subject years. Review of the data from long term continuation studies with belimumab does not suggest a signal for increased risk of malignancies in association with cumulative exposure. <u>BEL115471</u> Malignant neoplasm AESI reported during the double-blind phase of this study was a solid tumor (squamous cell carcinoma of the cervix), which occurred in 1 subject (0.3%) in the belimumab group. <u>BEL116027</u> In this study of 80 patients, no AESIs for malignant neoplasms were reported for any subject in any group. <u>BEL115467</u> In this study of 4,003 subjects with SLE (1:1 randomization), the incidence of malignant neoplasms was similar between treatment groups during the on-treatment period. Malignancies including NMSC were reported in 8 (0.4%) subjects in the placebo group and 9 (0.4%) subjects in the belimumab 10 mg/kg group. Malignancies excluding NMSC were reported in 5 (0.2%) subjects in the placebo group and 5 (0.2%) subjects in the belimumab group. Malignancies reported during the on treatment period consisted of solid tumors (5 [0.2%] placebo, 4 [0.2%] belimumab), hematologic (0 placebo, 1 [<0.1%]

Potential Risk: Malignancies	
	belimumab), and NMSC (3 [0.1%] placebo, 4 [0.2%] belimumab). The results for malignant neoplasm during the on-study period were similar to the on-treatment period with no clinically meaningful differences observed between treatment groups. During the on-study period, malignancies including NMSC were reported in 10 (0.5%) subjects in the placebo group and 9 (0.4%) subjects in the belimumab 10 mg/kg group. Malignancies excluding NMSC were reported in 7 (0.3%) subjects in the placebo group and 5 (0.2%) subjects in the belimumab group during the on-study period. Following the 1-year treatment period (Year 1), the BEL115467 study continued to follow participants for a further 4 years (Year 2-5). The objective of the Year 2-5 follow-up period was to assess mortality and new primary malignancy, including NMSC, in adult SLE participants who received either belimumab plus standard therapy or placebo plus standard of care during Year 1 of the study. During the follow-up period, participants did not receive any investigational product as part of the trial and instead received physician-directed standard of care, which could have included commercially-available belimumab by prescription. Treatment group assignment was based on treatment received during the Week 52 double-blind treatment period. By the end of follow-up Years 2 and 3, the cumulative new primary malignancy participant incidence rate (per 100 participant-years) was numerically lower in the belimumab group compared with the placebo group. By the end of follow-up Years 4 and 5, the rates were similar between the treatment groups. By the end of Year 5 follow-up, the cumulative new primary malignancy participant incidence rate (per 100 participant-years) was 0.39 for the total study population (0.40 in the belimumab group and 0.38 in the placebo group). This is consistent with and numerically lower than the reported malignancy rate of 0.53 per 100 person-years for an international cohort of 16 409 SLE patients who were followed from 1958 to 2009 [Bernatsky, 2013]. The proportion of participants who reported a new primary malignancy for follow-up Years 3 and 4 (0.52% and 0.47%, respectively) was comparable to the proportion during the controlled treatment period in Year 1 (0.47%). The proportion of participants who reported a new primary malignancy in follow-up Years 2

Potential Risk: Malignancies	
	and 5 (0.30% and 0.16%, respectively) was lower than Year. Overall, the data suggest that belimumab treatment during Year 1 did not increase risk for new primary malignancies during the follow-up period. The new primary malignancy safety data for the Year 2-5 follow-up period did not present new safety concerns for the use of belimumab in patients with active, autoantibody-positive SLE who received standard therapy. <u>BEL114054</u> This phase 3 study evaluated the efficacy and safety of belimumab plus standard of care versus placebo plus standard of care in 448 adult subjects with active lupus nephritis. The double blind phase has completed. There were no malignancies reported in the placebo group. The incidence of malignancies in the belimumab group was 1.3% (3 subjects). The events occurred on treatment and were one case each of basal cell carcinoma (non-melanoma skin cancer; / azathioprine), papillary thyroid cancer (solid tumor; mycophenolate mofetil), and thymoma (tumor of unspecified malignancy adjudicated as malignant; mycophenolate mofetil). Overall, no trends were observed for any malignant neoplasm category. The open label extension has completed. There were no malignancies reported during the open-label phase. Malignancies (including NMSC) will continue to be evaluated during the ongoing 5 year observational safety registry (SABLE).
Severity and nature of risk	Most malignancies are considered serious and are not self-limited in growth. The outcome depends on the type of malignancy, time to diagnosis, other ongoing conditions and available treatment. Some malignancies can resolve with treatment. Across all completed IV and SC SLE studies (including LN) through 08 March 2024, there were 3 events of fatal malignancy in the belimumab group (one report each of lymphoma of the left breast and large b-cell lymphoma both possibly related to belimumab, and one report of ovarian cancer not related to belimumab). There were no events of fatal malignancy in the placebo group.

Potential Risk: Malignancies	
Background incidence/prevalence	SLE is associated with an increased risk for certain cancers. In an international cohort of 16,409 patients from 30 centres with an average follow-up of seven years (121,283 patient-years), 644 cases of cancer (excluding NMSC) were observed for an overall incidence rate of 0.53 per 100 patient-years. [Bernatsky, 2005]. Results from this analysis suggest an increased risk among patients with SLE for hematological cancers (non-Hodgkin's lymphoma; NHL and leukemia) as well as lung cancer and thyroid cancer. The increased cancer risk among SLE patients compared with the general population was driven primarily by the 3 to 4-fold higher incidence of hematological malignancies, including NHL.
Risk groups or risk factors	Patients with SLE typically receive a wide variety of immunosuppressive or cytotoxic agents which confer an increased risk of developing malignancy. Bernatsky et al. conducted a separate analysis in a subset of collaborating centres (n=15) to evaluate the association between exposure to immunosuppressive therapy (cyclophosphamide, azathioprine, methotrexate) and cancer risk. In this nested case-control study, adjusted hazard ratio estimates for hematological cancers associated with immunosuppressive exposure was hypersensitivity reaction 2.29 (95% CI: 1.02-5.15) in a timeframe of up to 5 years post-exposure though further research is needed to delineate the risks associated with disease activity and immunosuppressant exposure [Bernatsky, 2008]. Thus, the natural history of SLE appears to predispose patients to developing malignancies, as may its current treatments. In an international cohort study [Bernatsky, 2013], there was a suggestion of higher lymphoma risk among SLE patients with exposure to cyclophosphamide and high cumulative steroids. In univariate analyses and a partially adjusted model (where covariates included age, sex, Sjogren's, cyclophosphamide, cumulative steroid and disease activity) a twofold increased risk of lymphoma was observed with both cyclophosphamide exposure and cumulative steroid of at least 3.5 g. Although the parameter estimate was elevated (HR) in the fully adjusted model, the CI included the null value for both cyclophosphamide exposure (HR 2.80, 95% CI: 0.87-8.98) and cumulative steroid of at least 3.5 g (HR 2.57, 95% CI:

Potential Risk: Malignancies	
	0.94-7.04). High disease activity (mean adjusted SLEDAI-2K ≥6 or the highest quartile of the mean adjusted activity score if another index was used) itself was not clearly associated with lymphoma (HR 0.68, 95% CI: 0.39-1.29).
Potential mechanisms	Malignancies are a theoretical concern with all immunomodulatory biologics; however, the preclinical experience with belimumab does not support a pro-oncogenic effect. Given the targeted mechanism of action, the probability that belimumab confers a direct risk of malignancy mediated through general immunosuppression appears low. A literature review of the potential involvement of BLyS in tumor biology has not revealed evidence to suggest ablation of BLyS would lead to the transformation of normal cells. It has been shown that serum BLyS levels are elevated in a subgroup of patients with NHL. In patients with de novo large B-cell lymphoma, a high BLyS level correlated with a poorer median overall survival [Novak, 2004]. Therefore in this instance reduction of BLyS could be considered beneficial. In addition, there are data available from mice (A/WySNJ) that have a non-functional BR3/BAFF-R receptor. The phenotype of the A/WySNJ mice strain is very similar to the BlyS-knockout mice and is caused by an insertion in the BR3/BAFF-R gene that results in a non-functional receptor and mature B cell deficiency. Aged (22 months) A/WySNJ mice do not have a higher rate of infection or neoplasia than their co-isogenic A/J counterparts, or other mouse strains routinely used for aging studies, supporting the conclusion that BLyS inhibition does not increase the risk of infection or neoplasia in animal models. Finally, no proliferative or pre-neoplastic changes were reported in any of the monkeys in a 6-month repeat dose toxicology study with an accompanying 8-month recovery period (Report 1177-95; Section 2.6.6.3.2; sequence 0000).
Preventability	Unknown
Impact on individual patient	Most malignancies are considered serious and are not self-limited in its growth. The impact on patients depends on type and location of the malignancy. Some

Potential Risk: Malignancies	
	Malignancies can result in significant pain and long-term treatment and can affect morbidity and mortality.
Potential public health impact of safety concern	Unknown
Evidence source	Data are referenced in the Clinical Summary of Safety (see Module 2.7.4 sequence 0135).
MedDRA terms	Malignancies SMQ and Malignant lymphomas SMQ

SVII.3.2 Presentation of the missing information

Risk	What is known
Limited data in pregnant and lactating patients	There have been a low number of pregnancy cases so far in patients taking belimumab, so it is difficult to assess whether taking belimumab increases the risks of an unsuccessful pregnancy. Belimumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If prevention of pregnancy is warranted, women of childbearing potential should use adequate contraception while using belimumab and for at least 4 months after the last belimumab treatment. A patient must tell her doctor if she becomes pregnant whilst taking belimumab, or up to 4 months after stopping treatment with belimumab. <u>BEL114256/BPR</u> A global belimumab "pregnancy registry" (BEL114256) was set up to collect information on a voluntary basis in women with SLE who received belimumab within 4 months prior to and/or during pregnancy. Exposure is defined as a minimum of one complete or partial dose of commercial belimumab within the 4 months prior to and/or during pregnancy. The registry also collected information up to 1 year on the infants born to mothers taking belimumab. The prospective cohort was the primary analysis cohort, and the primary endpoint was birth defects. Secondary endpoints included spontaneous miscarriage, live birth (including preterm birth, small-for-gestational-age [SGA], and neonatal death), stillbirth, elective termination, molar pregnancies, ectopic pregnancies and serious and/or clinically significant infections in infants through one year of age. Birth defects were defined and coded in the primary analysis with criteria specified by the Centers for

Risk	What is known
	Disease Control and Prevention (CDC)'s Metropolitan Atlanta Congenital Defects Program (MACDP). Because the BPR was conducted in North America and Europe, the BPR used the European Surveillance of Congenital Anomalies (EUROCAT) in addition to the US-based CDC MACDP in subgroup analyses. Enrollment ceased on 28 October 2022. The BPR sought to enroll approximately 500 prospective pregnancies exposed to commercially supplied belimumab. At the time of BPR closure, 72 participants (61 prospective, 11 retrospective) were enrolled with a confirmed outcome. Pregnancy loss occurred in 4 of 61 prospective pregnancies (6.6%, 95% CI 0.3%-12.6%) with 3 miscarriages and 1 stillbirth (no elective terminations were reported). When restricting to pregnancies enrolled prior to 20 weeks' gestation, the fetal loss occurrence rate in the BPR was 3/57 (5.3%, 95% CI 0.0%-10.9%). Of the 61 prospective pregnancies with known outcomes, 58 resulted in a live birth with 61 live infants. Preterm birth occurred in 19 (31.1%, 95% CI: 19.5%-42.8%) of 61 live birth infants Four (6.6%) infants were considered SGA based on INTERGROWTH-21st criteria and 12 (19.7%) infants were considered SGA based on Alexander criteria. Of the 61 live birth infants in the prospective cohort, 4 (6.6%, 95% CI 0.3%-12.8%) reported a serious infection during the first year of life (viral meningitis, endocarditis, respiratory syncytial virus occurring in 1 infant each, rhinovirus and gastroenteritis both occurring in the same infant). All serious infections resolved. Sixteen non-serious clinically-significant infections were reported in 14 (23.0 %) infants during the first year of life. Fourteen of the events were resolved, 1 was ongoing and the status of 1 was unknown. The prevalence of birth defects (using MACDP definition) reported in the primary study population (live birth infants from prospectively enrolled pregnancies) of the BPR is 18% (11/61, 95% CI 8.4%-27.7%). The wide confidence interval suggest imprecision in the prevalence estimates and, as such, should be interpreted with caution. Prevalence estimates varied based on the defect criteria used with a prevalence of 19.7% (12/61, 95% CI 9.7%-29.6%) using either MADCP or EUROCAT definitions.

Risk	What is known
	Reported birth defects include: 1) mild Ebstein anomaly, 2) bilateral club foot, 3) complete heart block (with anti-Ro and/or anti-LA antibodies), 4) ventricular septal defect (VSD) and congenital hydronephrosis (both spontaneously resolved within 15 months) in 1 infant, 5) VSD identified in utero, but not at birth, and small fenestrated atrial septal defect noted at birth in 1 infant, which closed within 10 months after birth, 6) Arnold-Chiari malformation, 7) Congenital spinal cord anomaly (low lying conus medullaris) and congenital pyelocaliectasis in 1 infant, 8) three reports of plagiocephaly and torticollis in 3 infants, 9) undescended testicle, and 10) ankyloglossia. Seven defects from 4 infants were considered to be defects of known cause or no temporal association (1 bilateral club foot, 3 positional plagiocephaly, and 3 torticollis), as these may occur due to mechanical factors during the pregnancy (Moh, 2012; Sharon- Weiner, 2017). Congenital heart block, which was observed in 1 infant in this study, is also a defect of known cause as it is known to be associated with SLE and anti-Ro/SSA and anti-La/SBB antibodies (Buyon, 2015; Lateef & Petri, 2013), the presence of which had been confirmed in this participant by laboratory testing. One infant case of undescended testicle may not have been exposed to belimumab during the critical window of development. There were missing defect details (e.g., septal size) that are required to properly classify as a major defect for the infant case with ventricular septal defect. Additionally, there is no reason to predict an IgG antibody would affect interventricular septum development (which completes by seven weeks in humans) because belimumab is highly specific for BLyS, which binds to receptors primarily localized to B lymphocytes, and because there is very little placental transfer of IgG antibodies during the first trimester (Dhanantwari et al., 2009; Simister, 2003). A total of 11 retrospective pregnancies were enrolled within the BPR of which none resulted in a major birth defect as well a no serious infections or non-serious clinically-significant infections during infant 1 year follow-up. Pregnancy loss, excluding elective termination, occurred in 40% (4/10) pregnancies for participants completing the registry. These results should be interpreted with caution as the retrospective reports would be subject to biases since pregnancy outcome was known prior to enrollment.

Risk	What is known
	Limitations of the BPR, including low enrollment and no comparator, resulted in imprecise estimates for the study outcomes making it challenging to draw inferences on the available data. The Belimumab Scientific Advisory Committee (SAC) of external clinical researchers independently reviewed all data reported to the BPR as well as supplemental data and concluded that there are insufficient pregnancy outcomes to ascertain the risks of birth defects and the secondary endpoints of intent for pregnancy exposed to commercially supplied belimumab. <u>The Belimumab & Lupus Pregnancy Study</u> (213928/bMUM) in the US and Canada has replaced the global belimumab pregnancy registry and will evaluate pregnancy outcomes in women with SLE as well as infant outcomes through 1 year. This study will collect information on a voluntary basis for both Benlysta exposed and unexposed pregnancies. Data from the closed pregnancy registry (BEL114256/BPR) will be utilized as supportive information. <u>GSK Safety Database</u> Pregnancy reports received within the GSK Argus Safety Database through 08 March 2024, included 220 from belimumab clinical trials (187 belimumab, and 33 placebo), and 659 from literature, spontaneous reports and PMS studies outside of the non-interventional pregnancy studies. Pregnancy reports were excluded from the above counts if they were of child cases in which the pregnancy was reported in the maternal or twin case, no exposure to belimumab during the pregnancy, partner pregnancy with no apparent congenital anomaly as outcome, report was not a report of pregnancy, duplicate pregnancy case, egg donor exposure to belimumab and pregnancies from non-GSK sponsored clinical trials. Four of the 187 belimumab-exposed clinical trial pregnancy reports were from the lupus nephritis study (BEL114054). One pregnancy was lost to follow-up while the other 3 pregnancies ended in elective termination. Embryo damage was reported as a congenital anomaly in 1 of these three pregnancies. One belimumab-exposed clinical trial pregnancy occurred during study 209629 conducted in Chinese healthy participants. The pregnancy ended in elective termination with no congenital anomaly.

Risk	What is known
	The remaining 182 pregnancies were reported in SLE patients. Of the total belimumab-exposed pregnancies with known outcomes excluding elective terminations (n=112), the rate of spontaneous abortion was 33/112 (29.5%) and the rate of stillbirths was 2/112 (1.8%). Among pregnancies in the placebo group, out of 21 pregnancies with known outcomes excluding elective termination, the rate of spontaneous abortion was 7/21 (33.3%) and the rate of stillbirths was 1/21 (4.8%). Among belimumab-exposed pregnancy reports there have been 4 live infants exposed to belimumab in utero reported with congenital anomalies from clinical trials with the proportion of congenital anomalies among pregnancies ending in live birth being 4/74 (5.4%) [Live births with congenital anomalies/Live births]. No congenital anomalies were reported in live infants of mothers in the placebo group. The congenital anomalies in live infants reported to date in clinical trials include 1) unbalanced translocation involving chromosomes 11/13 with microcephaly and AVSD, 2) Dandy Walker Syndrome, 3) Bilateral enlarged kidneys with severely abnormal function and positional deformities of the head and extremities and 4) pulmonic stenosis. Outside of the clinical trial program, 659 belimumab-exposed pregnancy reports were received from post-marketing sources: literature, spontaneous sources and post-marketing surveillance studies (outside of the non-interventional pregnancy studies [BPR and bMUM]). Of the total pregnancies with known outcomes excluding elective terminations (n=272), the rate of spontaneous abortion was 73/272 (26.8%) and the rate of stillbirths was 4/272 (1.5%)The total number of pregnancies ending in live birth was 192. Six of these pregnancies were twin pregnancies for a total of 198 live infants. Of 192 pregnancies ending in live birth, there have been 3 live births reported with congenital anomalies from post-marketing sources with the proportion of congenital anomalies being 3/192 (1.6%). The congenital anomalies in live infants reported to date in post-marketing sources include: 1) extrarenal pelvis, 2) Chondroectodermal dysplasia with congenital nose malformation, cleft palate, hemivertebra, brachycephaly,

Risk	What is known
	and congenital bowing of long bones; and 3) Congenital pyelocaliectasis. Two spontaneous reports of congenital anomalies in 2 stillborn fetuses were received. These included 1) congenital hydrocephalus and 2) Trisomy 21 and AVSD. One spontaneous report of an unspecified congenital anomaly was reported for a spontaneous abortion. This report was not medically confirmed. The reporter mentioned Turner's Syndrome and Trisomy 21 but was not clear. The BPR SAC, an independent advisory committee, reviewed birth defect cases through 08 March 2021. Additionally, GSK, including an internal GSK pregnancy expert panel, independently reviewed birth defect cases received across all sources through 08 March 2023 in terms of embryological or biological considerations. No new reports of congenital anomalies were received between 09 March 2023 and 08 March 2024. Following GSK's assessment of birth defects reported in belimumab-exposed pregnancies across all data sources, GSK, including an internal GSK pregnancy expert panel and consistent with the BPR SAC, concludes there were not novel defects or multiple defects of a common nature or type that would suggest an unusual pattern or common mechanism of birth defects in individuals receiving belimumab. <u>Lactation</u> Cumulatively through 08 March 2024, there were 21 reports of exposure to belimumab during breastfeeding, all of which were spontaneous or post-marketing reports (including BPR reports). In one case, the neonate had been born premature and spent 70 days in the intensive care unit. No further AE/SAEs were reported for the infant. In another case, head tilt was noted in the infant at 4 months and noted by the neurologist to be either behavioral or benign paroxysmal torticollis. This was not considered a defect, and the neurologist noted it would resolve spontaneously if it was benign paroxysmal torticollis. In another case, the mother received 1 dose of belimumab, and the infant had eye surgery for an

Risk	What is known
	unknown reason. One infant experienced unexplained poor weight gain with no other health problems. In another case, the mother did not produce enough breast milk resulting in the infant being hospitalized for low blood glucose and weight loss. The infant was provided with formula and the weight loss resolved. The infant also received oxygen therapy which has resolved. Another infant experienced torticollis and acquired plagiocephaly (defects reported above under BPR results) which were diagnosed at the four-month doctor check-up following exposure to belimumab via breast milk during at least the first month. At 10 months old, the infant experienced otitis media and febrile infection No AEs were reported for the remaining neonates exposed to belimumab in breastmilk.
Limited data in elderly patients	The number of elderly subjects was small (N=63), 1.5% of the all subjects population (N=4170) in the pooled elderly population from the CRD studies LBSL02, C1056, C1057, BEL113750, BEL115471, and BEL112341, so there is limited information on the safety and efficacy of belimumab in elderly patients. Safety and efficacy results presented in the elderly SLE population are generally consistent with what was observed in the broader SLE population. However, due to the relatively limited number of elderly patients studied, belimumab should be used with caution in elderly SLE patients. Although data are limited, dosage adjustment is not recommended. The MAH has committed to providing data on the elderly through periodic pooled analyses. The purpose of these pooled analyses is to evaluate safety and efficacy data from the elderly (age ≥65 years) subpopulation treated in selected belimumab studies.
Lack of data in SLE patients with severe active CNS lupus.	CNS lupus is lupus related to the nervous system. Patients with severe lupus linked to the nervous system were not included in patient studies, as they are more likely to require more complicated (non-standard) treatment. Therefore, information for these patients is very limited.
Limited data on long-term safety in pediatric patients	The indication for the IV product has been extended to children with SLE aged 5-17 years. The double-blind phase of study BEL114055 has completed. A total of 93 subjects (40 subjects in the placebo group, 53 subjects in the belimumab 10 mg/kg group) received at least 1 dose of study agent during the double-phase. Safety findings

Risk	What is known
	were consistent with the 5 large adult efficacy and safety double-blind randomized controlled trials, and no new safety signals were identified in children with SLE [Brunner, 2020; Brunner, 2021]. The AE and SAE profile of IV belimumab in children was comparable to placebo in BEL114055 and consistent with the observed profile of IV belimumab in the adult SLE studies. Incidence of infections and serious infections was lower in the belimumab group compared with placebo, and comparable to the incidences reported in the adult SLE studies. No clinically meaningful differences in infections of special interest were observed between treatment groups in study BEL114055. Although herpes zoster AEs occurred more frequently in the belimumab group, serious herpes zoster events were uncommon, and the incidence was similar between groups. There were no reported cases of PML, serious opportunistic infections, malignancies, or suicidality. Safety data collection is ongoing in the open label extension phase of BEL114055 (Part B) which continues in children with SLE for up to 10 years after their first belimumab dose. Part B has been ongoing since 2013, no new safety findings identified to date.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 9 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infections Psychiatric events including depression and suicidality
Important potential risks	Progressive multifocal leukoencephalopathy Malignancies
Missing information	Limited data in pregnant and lactating patients Limited data in elderly patients Limited data on long-term safety in pediatric patients Lack of data in SLE patients with severe active CNS lupus

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORIZATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are required:

Specific adverse reaction follow-up questionnaires for Progressive Multifocal Leukoencephalopathy:

Ofatumumab/ Belimumab & Progressive Multifocal Leukoencephalopathy (PML)

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)

Specific adverse reaction follow-up questionnaires on infections for pediatric patients 5 to 11 years of age:

Belimumab and Infections

III.2 Additional pharmacovigilance activities

A number of imposed and additional pharmacovigilance activities to address specific safety concerns have either been completed or are planned/ongoing for belimumab. Brief summaries are provided below for ongoing activities).

PAM category 1-3 studies:

PLUTO Pediatric SLE Intravenous Formulation Study

A Multi-center, Randomized Parallel Group, Placebo-Controlled Double-Blind Trial to Evaluate the Safety, Efficacy, and Pharmacokinetics of Belimumab, a Human Monoclonal Anti- BLyS Antibody, Plus Standard Therapy in Pediatric Patients with Systemic Lupus Erythematosus (SLE).

Rationale and study objectives:

The objectives of this study are to evaluate the safety and tolerability, pharmacokinetics and efficacy of belimumab in the pediatric SLE population and to evaluate the effects of belimumab on the quality of life in the pediatric SLE population. Part A has competed and was a randomized, placebo-controlled, double-blind 52-week treatment phase to evaluate the efficacy, safety, and pharmacokinetics of 10 mg/kg belimumab intravenous (IV) in pediatric subjects with active SLE. Following completion of Part A, participants entered into Part B (long term belimumab open label safety follow up phase) or Part C (long term safety follow up phase).

Study design:

Part A - Randomized, placebo-controlled, double-blind 52-week treatment phase.
Part B - Long term belimumab open label safety follow up for any subject who completed Part A
Part C - Long term safety follow up phase for subjects who withdraw from Part A or Part B at any time.

Study population:

Males and females 5 to 17 years of age with a clinical diagnosis of active, autoantibody positive SLE and are on an SLE treatment regimen as outlined in the protocol inclusion criteria. Participants were excluded if they received treatment with belimumab at any time, received treatment with any of the medications outlined in the protocol exclusion criteria, have active CNS lupus, acute severe nephritis, history of malignant neoplasm within 5 years, evidence of serious suicide risk in participants ≥12 years of age, required management of acute or chronic infections, known HIV infection, hepatitis B or hepatitis C infection or other conditions outlined in the protocol exclusion criteria.

Milestones:

Final CSR: 31Dec2028.

SABLE Safety Registry

A 5-Year Prospective, Observational Registry to Assess Adverse Events of Special Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without Benlysta (Belimumab).

Rationale and study objectives:

The primary objectives are to evaluate the incidence of the following adverse events of special interest: malignancies (excluding non-melanoma skin cancer), mortality, opportunistic infections and other infections of interest, non-melanoma skin cancer, selected psychiatric events, and serious infections.

Study design:

Multi-centre, prospective, observational, cohort study.

Study population:

Males or females age 18 or older, have a clinical diagnosis of SLE, current or history of autoantibody-positive SLE, must be treated with SLE therapy, including Benlysta. Patients are excluded if they have received treatment with an investigational drug within one year of enrolment, currently enrolled in a placebo-controlled Benlysta clinical trial or a

continuation protocol where belimumab is used as an investigational agent; patients who have a history of Benlysta exposure but are not currently receiving Benlysta; patients only receiving an antimalarial or steroids for SLE.

Milestones:

Yearly interim reports from 28Feb2014 through 28Feb2021. A further interim report 28Feb2023. Final CSR 28Feb2026.

Belimumab & Lupus Pregnancy Study (213928/bMUM)

Rationale and study objectives:

This is a prospective, observational, exposure cohort study in the United States and Canada of pregnancy outcomes in women exposed to belimumab during pregnancy (from 3 months prior to the first day of the last menstrual period (LMP) throughout pregnancy) compared to pregnancy outcomes in women with a diagnosis of SLE who have not used belimumab and may or may not have used other medications for the treatment of their disease during pregnancy (disease comparison group). The registry relies on voluntary reporting of pregnancy and exposures by women and health care providers who contact the North American Organization of Teratology Information Services /MotherToBaby (OTIS-MTB) network of teratogen information counselling services. Objectives are to monitor planned and unplanned pregnancies exposed to belimumab and to evaluate the possible teratogenic effect of this medication relative to the primary outcome of major birth defects. Secondary outcomes also evaluated in the study include other pregnancy outcomes (spontaneous abortion (including ectopic and molar pregnancies), stillbirth, elective termination, preterm delivery) as well as infant outcomes (pattern of minor malformations, small for gestational age at birth, postnatal growth deficiencies, and serious or opportunistic infections in live born infants up to one year of age). This study has replaced the pregnancy registry (BEL114256/BPR).

Study design:

Prospective cohort study. This study is designed to serve as an early warning system to identify a previously unrecognized major teratogen by identifying major birth defects in infants of exposed mothers. A stepwise approach will be used for the analysis. The initial analysis will be descriptive and unadjusted. Due to the observational nature of the study, where numbers permit, multivariable analyses will be conducted for the primary and secondary analyses to adjust for possible confounders.

Study population:

Cohort 1: Currently pregnant women diagnosed with SLE who have been exposed to belimumab from 3 months prior to the first day of the LMP up to and including the end of pregnancy.

Cohort 2: Currently pregnant women diagnosed with SLE who were not exposed to belimumab from 3 months prior to LMP or anytime during pregnancy.

Milestones:

Final CSR: 31May2030.

Pooled Analysis of Belimumab Elderly Patients

Rationale and study objectives:

Pooled analyses of elderly (aged ≥65 years) subpopulation treated in select completed and ongoing IV and SC belimumab clinical trials. The primary objective is to evaluate the safety of belimumab treatment in elderly patients with SLE.

Study design:

Pooled data from the following belimumab studies: LBSL02, HGS1006-C1056, HGS1006-C1057, BEL113750, HGS1006-C1115, and BEL115471 in addition to BEL115467.

Study population:

The primary population is defined as the subpopulation of elderly patients (aged ≥65 years at baseline) who were randomized and received at least one dose of study agent from the studies: LBSL02, HGS1006-C1056, HGS1006-C1057, BEL113750, HGS1006-C1115, BEL115471, and BEL115467.

Milestones:

Report 1: Sep2013; Report 2: Jul2016; Report 3: Jul2017; Report 4: Dec 2019; Report 5: Feb2026.

III.3 Summary Table of additional Pharmacovigilance activities

Table 10 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
5-Year Safety Registry HGS1006-C1124 (BEL116543/SABLE) Ongoing	To provide a data report on a long-term controlled safety registry where all patients are followed for a minimum of 5 years, based on a protocol agreed with CHMP. The safety registry will evaluate the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus. These adverse events of special interest include serious infections (including opportunistic infections and PML), selected serious psychiatric events, and malignancies (including non-melanoma skin cancer).	Infections (including PML), Psychiatric events including depression and suicidality, Malignancies	Final CSR	28Feb2026
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
None				
Category 3- Required additional pharmacovigilance activities				
Belimumab and Lupus Pregnancy Study (213928/bMUM) Ongoing	Prospective cohort study of Benlysta exposed and unexposed pregnancy. Primary objectives are to evaluate pregnancy and infant outcomes following Benlysta exposure and health status of live infants at 1 year.	Limited data in pregnant patients	Final CSR	31May2030
Elderly Subject Analyses BEL116559 Ongoing	Pooled analyses of elderly patients (aged ≥ 65 years) who participated in select belimumab clinical trials	Limited data in elderly patients	Report 5	Feb2026
Pediatric SLE IV Formulation Study BEL114055/PLUTO-open label Ongoing	To evaluate the safety and tolerability, pharmacokinetics and efficacy of belimumab and the effects of belimumab on the quality of life in the pediatric SLE population.	Infections, Limited data on long-term safety in pediatric patients	Final End of Study CSR	31Dec2028

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are currently no imposed post-authorization efficacy studies for belimumab.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table 9 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Infections	**Routine risk communication:** SmPC Sections 4.4, 4.8 **Other routine risk minimization measures beyond the Product Information:** This is a prescription only medicine.
Progressive Multifocal Leukoencephalopathy	**Routine risk communication:** SmPC Section 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** The IV and SC SmPC Section 4.4 Special warnings and precautions for use of the SmPCs contains text noting PML has been reported with Benlysta treatment for SLE and patients should be monitored for PML. Recommendations for HCPs regarding monitoring and what to do if PML is suspected are provided. **Other routine risk minimization measures beyond the Product Information:** This is a prescription only medicine.
Malignancies	**Routine risk communication:** SmPC Section 4.4 **Other routine risk minimization measures beyond the Product Information:** This is a prescription only medicine.
Psychiatric events including depression and suicidality	**Routine risk communication:** SmPC Sections 4.4, 4.8

	Other routine risk minimization measures beyond the Product Information: This is a prescription only medicine.

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimization measures

Table 10 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Important Identified Risks		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Infections	Routine risk minimization measures: SmPC Sections 4.4, 4.8 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 on infections for patients 5 to 11 years old. Additional pharmacovigilance activities: 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)

Important Identified Risks		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
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: None	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 randomized controlled trials and BEL116543/SABLE (5-year registry study)

Important Potential Risks		
Safety concern	**Risk minimization 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 text noting PML has been reported with Benlysta treatment for SLE and patients should be monitored for PML. Recommendations for HCPs on what to do if PML is suspected are provided.	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 Additional pharmacovigilance activities: • Evaluation of data on opportunistic infections, including PML, tuberculosis, and herpes zoster from long-term

Important Potential Risks		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
	This is a prescription only medicine. Additional risk minimization measures: None	safety registry (BEL116543/SABLE)
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 Additional pharmacovigilance activities: • Evaluation of data on malignancies, including hematologic malignancies and NMSC from the long-term safety registry (BEL116543/SABLE)

Missing Information		
Safety concern	**Risk minimization 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 Belimumab & Lupus Pregnancy Study (213928/bMUM) in the United States and Canada that has replaced the Benlysta Pregnancy Registry (BEL114256)

Missing Information		
Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
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 pediatric 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: • Specific adverse reaction follow-up questionnaires on infections for pediatric patients 5 to 11 years of age Additional pharmacovigilance activities: • Evaluation of long-term safety (adverse events of special interest, including infections, other autoimmune disease, immunogenicity, and malignancies) in subjects in BEL114055 until 10 years after their first belimumab dose •
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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for BENLYSTA (belimumab)

This is a summary of the risk management plan (RMP) for Benlysta. The RMP details important risks of Benlysta, how these risks can be minimized, and how more information will be obtained about Benlysta's risks and uncertainties (missing information).

Benlysta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Benlysta should be used.

This summary of the RMP for Benlysta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Benlysta's RMP.

I . The medicine and what it is used for

Benlysta is authorized

- as an 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. anti-dsDNA and low complement) despite standard therapy
- in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis (LN)

Benlysta is available as a subcutaneous injection (SC) or an infusion (IV). The IV route and SC route via the pre-filled pen formulation are approved for use in patients aged 5 years and older with SLE and adult patients with active lupus nephritis, whilst the SC route via the pre-filled syringe is approved only in adults with SLE and adult patients with active lupus nephritis.

(see SmPC for the full indication). It contains belimumab as the active substance and it is given by IV or SC route.

Further information about the evaluation of Benlysta’s benefits can be found in Benlysta’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/benlysta

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Benlysta, together with measures to minimize such risks and the proposed studies for learning more about Benlysta's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Benlysta is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Benlysta are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered/taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Benlysta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Infections Psychiatric events including depression and suicidality
Important potential risks	Progressive multifocal leukoencephalopathy (PML) Malignancies

List of important risks and missing information	
Missing information	Limited data in pregnant and lactating patients Limited data in elderly patients Limited data on long-term safety in pediatric patients Lack of data in SLE patients with severe active central nervous system (CNS) lupus

II.B Summary of important risks

Important identified risk **Infections**	
Evidence for linking the risk to the medicine	Clinical trial and post-marketing data
Risk factors and risk groups	Infections are a common source of morbidity and mortality in patients with autoimmune diseases such as SLE. In addition to the disease itself, the use of immunosuppressive agents such as steroids and cytotoxic agents (e.g., cyclophosphamide, azathioprine, and MMF)
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.4, 4.8 This is a prescription only medicine. Additional risk minimization measures: None
Additional Pharmacovigilance activities	Additional Pharmacovigilance activities: 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) See II.C of this summary for an overview of the post-authorization development plan.

Important identified risk **Psychiatric events including depression and suicidality**	
Evidence for linking the risk to the medicine	Clinical trial, post-marketing data and literature
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.4, 4.8 This is a prescription only medicine. Additional risk minimization measures: None
Additional Pharmacovigilance activities	Additional Pharmacovigilance activities Prospective assessment of suicidality in randomized controlled trials and BEL116543/SABLE (5-year registry study) See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk **Progressive multifocal leukoencephalopathy**	
Evidence for linking the risk to the medicine	Clinical trial, post-marketing data and literature
Risk factors and risk groups	Infections, including PML, are common source of morbidity and mortality in patients with autoimmune diseases such as SLE. In addition to the disease itself, the use of immunosuppressive agents such as steroids and cytotoxic agents (e.g., cyclophosphamide, azathioprine, and MMF)
Risk minimization measures	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 text noting PML has been reported with Benlysta treatment for SLE and patients should be monitored for PML. Recommendations for HCPs regarding monitoring and what to do if PML is suspected are provided. This is a prescription only medicine. Additional risk minimization measures: None

Additional Pharmacovigilance activities	Additional Pharmacovigilance activities: Evaluation of data on opportunistic infections, including PML, tuberculosis, and herpes zoster from long-term safety registry (BEL116543/SABLE) See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk **Malignancies**	
Evidence for linking the risk to the medicine	Clinical trial, post-marketing data and literature
Risk factors and risk groups	Patients with SLE typically receive a wide variety of immunosuppressive or cytotoxic agents which confer an increased risk of malignancy.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 This is a prescription only medicine. Additional risk minimization measures: None
Additional Pharmacovigilance activities	Additional Pharmacovigilance activities: Evaluation of data on malignancies, including hematological malignancies and nonmelanoma skin cancer from the long-term safety registry (BEL116543/SABLE) See Section II.C of this summary for an overview of the post-authorization development plan.

Missing information **Limited data in pregnant and lactating patients**	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.6 and 5.3 This is a prescription only medicine. Additional risk minimization measures: None

Missing information **Limited data in pregnant and lactating patients**	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Ongoing Belimumab & Lupus Pregnancy Study (213928/bMUM) in the United States and Canada. See Section II.C of this summary for an overview of the post-authorization development plan.

Missing information **Limited data in elderly patients**	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 and 5.2 This is a prescription only medicine. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Analysis plan for BEL116559 has been agreed with EMA. See Section II.C of this summary for an overview of the post-authorization development plan.

Missing information **Limited data on long-term safety in pediatric patients**	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 This is a prescription only medicine. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Evaluation of long-term safety (adverse events of special interest, including infections, other autoimmune diseases, immunogenicity, and malignancies) in enrolled subjects in BEL114055 until 10 years after their first belimumab dose See Section II.C of this summary for an overview of the post-authorization development plan.

Missing information **Lack of data in SLE patients with severe active CNS lupus**	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 This is a prescription only medicine. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

SABLE Safety Registry:

Post-Marketing observational program for Benlysta (BEL116543)

Purpose of the Study:

To assess the effectiveness and safety of long-term treatment in patients receiving Benlysta compared to those who are not.

II.C.2 Other studies in post-authorization development plan

Pediatric SLE IV Formulation Study (PLUTO)

Part A has completed and was a randomized placebo-controlled treatment phase for pediatric patients with SLE (BEL114055). Part B is the ongoing long term belimumab treatment open label safety follow-up phase. Part C is the ongoing long term safety follow up phase following discontinuation of belimumab treatment in Part A or B.

Purpose of the Study:

To evaluate the safety and tolerability, pharmacokinetics and efficacy of intravenous belimumab in the pediatric SLE population and to evaluate the effects of belimumab on the quality of life in the pediatric SLE population.

Belimumab & Lupus Pregnancy Study (bMUM):

Prospective cohort study (213928/bMUM) of Benlysta exposed and unexposed pregnancies.

Purpose of the Study:

The primary objective is to evaluate pregnancy and infant outcomes following Benlysta exposure and health status of live born infants at 1 year.

Pooled Analysis of Belimumab Elderly Patients:

Pooled analyses of elderly patients (aged ≥ 65 years) who participated in select belimumab clinical trials (BEL116559)

Purpose of the Study:

To determine the safety and effectiveness in elderly patients.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

do more feel better live longer	**Targeted Follow-Up Questionnaire** **BELIMUMAB & Progressive Multifocal Leukoencephalopathy (PML)**

Patient/subject ID, DOB/initials:	**Sex/weight (If weight unknown is patient obese?):**	**GSK CASE No:**

Lot Number & Expiration date (*for post-marketing reports only*):

Description of the Event:

Symptoms: *Please check all that apply.*

☐ limb weakness/ difficulty with ambulation *[Please specify]*

☐ cognitive deficits

☐ visual impairment

☐ Paralysis (Mono or hemiparesis*) [Please specify]*

☐ seizure

☐ Mental status changes (eg. decreased level of consciousness, confusion, coma (please describe):

	Yes	**No**
Were there any other signs of neurological changes?	☐	☐

If *yes*, please describe them briefly below:

Diagnostic Tests: *Please attach all applicable.*

Were any of the following investigations performed to confirm the diagnosis of PML? *Please check all that apply*.

☐ lumbar puncture for CSF JCV DNA (Circle) positive or negative for JCV DNA

☐ Brain biopsy

☐ MRI of the brain (Provide results)

☐ Serum JCV DNA

☐ CD 4 Count

☐ IgG level

Other diagnostic test/s, (eg. Nerve conduction studies, serology testing) if available:

How was the PML treated?

What was the outcome?

	Yes	**No**
Was a neurology consult completed? If yes please include copy of consult with this form.	☐	☐

History:

	Yes	**No**
Did the patient have a history of neurological disease? If *yes*, please provide details.	☐	☐
Was the subject diagnosed with disease with impaired immune response (e.g. immunodeficiency syndrome, HIV infection, systemic lupus erythematosus, malignancy)? If *yes*, please provide details (date of diagnosis)	☐	☐
Did the patient have a history of organ transplant? If *yes*, please provide details.	☐	☐
Did the patient have a history of chronic corticosteroid, immunosuppressive therapy or chemotherapy? If yes, please list medication name/s, dose(s), and duration of treatment.	☐	☐

Medication	**Dose**	**Duration of Treatment**

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

Targeted Follow Up Questionnaire
BELIMUMAB AND POSSIBLE SUICIDAL BEHAVIOR/SUICIDAL IDEATION (INCLUDING POTENTIAL SELF HARM such as INTENTIONAL OVERDOSE)

Patient/subject ID, DOB/initials:	**Sex/weight (is patient obese if weight unknown):**	**GSK CASE No:**

Lot Number & Expiration date (*for post-marketing reports only*):

Description of the Event:

Please indicate the possible causes of the suicidality-related or self-harm-related adverse event.	**Yes**	**No**
1. Was an actual suicide attempt made?	☐	☐
2. Were preparations for suicide made?	☐	☐
3. Was there a suicidal plan?	☐	☐
4. Did the subject express suicidal ideas before the event?	☐	☐
5. Was the subject known to be depressed or to express depressive thoughts before the event?	☐	☐
6. Were there co-morbid psychiatric condition(s:)		
a. Major Depressive Disorder	☐	☐
b. Psychotic Disorder	☐	☐
c. Personality Disorder (Axis II, DSMIV)	☐	☐
d. Other CNS illness including CNS lupus	☐	☐
7. Were there comorbid medical condition other than condition for which belimumab was given	☐	☐
8. Were there contributions of concomitant medication(s), discontinuation or dose change in medications	☐	☐
9. Was there the presence of illicit drugs or alcohol abuse or dependence?	☐	☐
10. Were there the presence of psycho-social stressor(s):	☐	☐
• Problems with family, friends or relationships	☐	☐
• Trouble at work	☐	☐
• Trouble with finances	☐	☐
• Trouble with the law or community	☐	☐
• Recent losses (death, loss of home, etc)	☐	☐

Description of the Event: Continued

Please indicate the possible causes of the suicidality-related or self-harm-related adverse event.	**Yes**	**No**

11. Was the subject known to be depressed or to express depressive thoughts after the event?	☐	☐
12. Was the patient seen by a psychiatrist?	☐	☐
13. Was the patient treated with antidepressants?	☐	☐
14. Was the patient known to have impulsive or attention-seeking behavior?	☐	☐
15. Has the patient had previous suicide attempts?	☐	☐
16. Has the patient previously been hospitalized for psychiatric reasons?	☐	☐
17. Has the patient previously been treated for depression?	☐	☐
18. Does the patient have a family history of suicide?	☐	☐

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Targeted Follow Up Questionnaire
Belimumab Infections

Patient/subject ID, DOB/initials:	Sex/wt:	GSK CASE No:	Date form completed:

Lot Number & Expiration date (*for post-marketing reports only*):

Description of the Event:

DATE OF INFECTION ONSET:

Infection Type: (e.g. pneumonia, endocarditis, etc) and location if relevant (e.g. subcutaneous abscess of the forearm or TB of the CNS)

What test(s) confirmed the infection (e.g., CXR, MRI, Echocardiogram, culture, clinical finding, etc)

Organism: (if organism is not known, enter 'unknown')

List all tests and results that attempted to confirm the organism itself? (blood culture, wound culture, PCR, gram stain, rapid antigen test, etc)

	Yes	No	Unknown
Did the infection resolve? If yes, when:_____	☐	☐	☐

	Yes	No
Was belimumab stopped as a result of this infection?	☐	☐
Was the infection present prior to starting belimumab?	☐	☐
If the belimumab was discontinued, was it subsequently restarted?	☐	☐

If *yes,* please specify date (DD/MM/YY) ☐☐/☐☐/☐☐:

Laboratory Tests

Please provide a summary of other relevant abnormal laboratory results (not previously listed above)

Treatment:

	Yes	No	Unknown
Was the patient hospitalized because of the infection?	☐	☐	☐
Was an antimicrobial used to treat the infection	☐	☐	☐

If yes, list all the antimicrobials used to treat infection:

RISK FACTORS (Check all that apply):	**Yes**		**Yes**
Alcohol abuse	☐	Occupational exposure	☐
Immobility	☐	Ostomy	☐
Recent SLE flare	☐	Post influenza	☐
Indwelling catheters	☐	Recent travel (ie, pandemic area)	☐
IV drug use	☐	Surgery < 30 days	☐
Nursing home resident	☐	TB exposure	☐
Smoker ☐ _____packs/day _____years			
Other:			

INFECTION HISTORY (check all that apply):	**Yes**	**No**	**Unk**	**If Yes, please specify**
Was the patient receiving any prophylactic antibiotic, antifungal, or antiviral agents?	☐	☐	☐	
Was the subject/patient receiving immunosuppressants?	☐	☐	☐	
Prior to receiving belimumab (or blinded product), did the patient experience any life-threatening infections?	☐	☐	☐	
Has the patient had any opportunistic infections in the past?	☐	☐	☐	

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ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Not applicable.