TITLE PAGE

Protocol Title: A Multi-Center, Open-Label Study to Evaluate Safety, Efficacy and Pharmacokinetics of Belimumab Plus Standard Therapy in Chinese Paediatric Patients with Active Systemic Lupus Erythematosus (SLE)

Protocol Number: 213560/Amendment 04

Compound Number:	GSK1550188

Study Phase: Phase 4

Short Title: Open label study of Belimumab plus standard therapy in Chinese Paediatric patients with active SLE

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Manufacturer: Not Applicable

Medical Monitor Name and Contact Information: The details will be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): Not applicable.

Sponsor Signatory:

Deepak Assudani, MD
Senior Clinical Development Director
Clinical Science (Immunology)
GSK

Approval Date: 22 Jan 2024

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 04	22 Jan 2024
Amendment 03	02 January 2023
Amendment 02	03 June 2022
Amendment 01	29 January 2021
Original protocol	27 October 2020

Amendment 04 22 Jan 2024

This amendment is considered non-substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it neither significantly impacts the safety of participants nor the scientific value of the study.

Overall Rationale for the amendment:

The purpose of this amendment is to add definitions for several terms to comply with an update to the internal GSK protocol process and template.

List of main changes in the protocol and their rationale:

Section # and Name	Description of Change	Brief Rationale
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	Addition or update of definitions for several terms, including Investigational Product, Standard of Care, Background treatment, Adverse Drug Reaction, SUSAR Move the section from 10.12 of previous version (amend 03) to the beginning of the protocol Delete Trademark Information	To comply with an update to the internal GSK protocol process and template.
10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments	Delele " References Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Participants. J Clin Microbiol. 2005;43(5):2363–2369."	Per new protocol template references should be added in Section 11. And the reference is not used in the document.
10.12. Appendix 12: Protocol Amendment History	Update section number from 10.13 to 10.12	Previous 10.12 have been moved to the beginning of protocol, adapted to update.
11. REFERENCES	Add belimumab IV injection prescribing information	To comply with an update to the internal GSK protocol process and template.

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
AST	Aspartate aminotransferase
AUC	Area under the curve
BLyS	B lymphocyte Stimulator
CCI	[redacted]
Cavg	Average plasma concentration
CBC	Complete blood count
CDE	Center for Drug Evaluation
CiC	Child in care
Cmin	The minimum blood plasma concentration reached by a drug prior to administration of a second dose
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CCI	[redacted]
CrCl	Creatinine clearance
CRD	Controlled Repeat Dose
CRP	C-reactive protein
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
dL	Decilitre
dsDNA	Double stranded deoxyribonucleic acid
eCRF	Electronic case report form
ECG	Electrocardiogram
EU	European Union
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GSK	GlaxoSmithKline
HB	Hepatitis B
HBsAg	Hepatitis B surface antigen
HBc	Hepatitis B core
HGS	Human Genome Sciences, Inc
HIV	Human immunodeficiency virus
HSR	Hypersensitivity reaction
IA	Intraarticular
IB	Investigator's Brochure
IM	Intramuscular
IEC	Independent ethics committee

CCI

IM	Intramuscular
INR	International Normalised Ratio
IRB	Institutional Review Board
ITT	Intention to Treat
IUD	Intrauterine device
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWRS	Interactive web response system
Kg	Kilogram
LDH	Lactate dehydrogenase
Mg	Milligram
mL	Millilitre
MCID	Minimally clinically important difference
MMF	Mycophenolate mofetil
MRI	Magnetic Resonance Imagery
MSDS	Materials Safety Data Sheet
NSAIDs	Non-steroidal anti-inflammatory drugs
ParentGA	Parent Global Assessment
PCR	Polymerase chain reaction
PGA	Physician Global Assessment
PD	Pharmacodynamic
PGx	Pharmacogenetics
PK	Pharmacokinetic
PO	By mouth (per os)
PT	Prothrombin time
PTT	Partial thromboplastin time
RA	Rheumatoid arthritis
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SC	Subcutaneous
SELENA	Safety of Estrogen in Lupus National Assessment
SFI	SLE Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SOC	System Organ Classes
SRI	SLE Responder Index
TACI Fc	Transmembrane activator attached to the Fc portion of an immunoglobulin
TNF	Tumour Necrosis Factor
ULN	Upper limit of normal
US	The United states

WOCBP	Woman of childbearing potential

TABLE OF DEFINITIONS

Term	Definition
Investigational Product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. 1. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries
Background treatment	Type of medicinal product administered to each of the clinical trial participant, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
Adverse Drug Reaction	An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions

	(ADRs) that are both serious and unexpected are subject to expedited reporting.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Multi-Center, Open-Label Study to Evaluate Safety, Efficacy and Pharmacokinetics of Belimumab Plus Standard Therapy in Chinese Paediatric Patients with Active **S**ystemic Lupus Erythematosus (SLE)

Short Title: Open label study of belimumab plus standard therapy in Chinese paediatric patients with active SLE

Rationale: The purpose of this study is to evaluate the safety, efficacy and pharmacokinetics of belimumab (10 mg/kg) intravenous (IV) with standard therapy in Chinese paediatric patients aged 5 to 17 years with active SLE. This study is conducted to support the registration of IV belimumab in treating paediatric SLE indication in China.

Objectives and Endpoints:

Objectives	Endpoints
Primary	**Primary**
➢ To evaluate the safety and efficacy of belimumab IV in Chinese paediatric patients with SLE.	Safety ➢ Incidence of adverse events of special interest (AESIs) through 52 weeks: • All Infections of special interest, including serious infections of special interest and opportunistic infections • Infusion related systemic reactions and anaphylactic reactions • Depression, suicidality • Malignancies Efficacy ➢ Incidence of patients with ≥4 points reduction from Baseline to Week 52 in SELENA SLEDAI
Secondary	**Secondary**
➢ To evaluate safety and tolerability of belimumab IV in Chinese paediatric patients with SLE	➢ Incidence of AEs through 52 Weeks ➢ Incidence of SAEs through 52 Weeks
➢ To evaluate the efficacy of belimumab IV in Chinese paediatric patients with SLE	➢ Incidence of patients with ≥4 points reduction from Baseline in SELENA SLEDAI by visit ➢ Change from Baseline to Week 52 in Physician Global Assessment (PGA)

Objectives	Endpoints
	➢ Change from Baseline to Week 52 in Parent Global Assessment (ParentGA) ➢ Change from Baseline in daily prednisone equivalent dose at Week 52 ➢ Time to first flare/ first severe flare over 52 weeks
➢ To evaluate the pharmacokinetics (PK) of belimumab (10 mg/kg) IV in Chinese paediatric patients with SLE	➢ Median belimumab concentration levels at Day 0, 7 and 14 days post first dose, and pre-infusion and post-infusion at Day 84 ➢ The PK will be evaluated with respect to clearance, volume of distribution and half-life, and individual steady state exposures Cmin, Cavg, Cmax and AUC.

AESI- adverse events of special interest, AUC- Area under the concentration curve, Cavg- average plasma concentration, IV- Intravenous, Cmin- the minimum blood plasma concentration reached by a drug prior to administration of a second dose, ParentGA - Parent Global Assessment, PGA- Physician Global Assessment, SELENA SLEDAI- Safety of Estrogen in Lupus National Assessment - Systemic Lupus Erythematosus Disease Activity Index

Overall Design: This is a multicentre, open label, single arm, prospective, 52-week study to assess the safety and efficacy of belimumab IV administered in combination with background standard therapy. The pharmacokinetics of belimumab will be assessed in a subset of participants.

Disclosure Statement: This is a single arm treatment study with no masking.

Number of Participants:

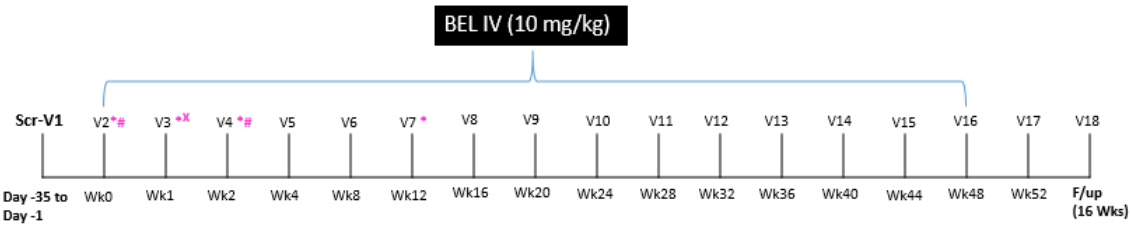
The sample size is justified by safety aim to capture the serious infection events as well by the purpose of evaluating efficacy in Chinese paediatric patients with active SLE. Focusing on adverse events (AEs) of serious infection, the incidence rate of the serious AEs of “Infections and Infestations” system organ class (SOC) was 7.5% in the 10 mg/kg-IV group of the phase II international joint study. Furthermore, for efficacy, the estimated percentage of subjects with ≥4-point reduction from Baseline in SELENA SLEDAI at Week 52 is 54.7%. Based on incidence rate of serious infections and efficacy endpoints in a previous study, approximately 65 participants are required to be enrolled in this study.

Note: "Screened" means that a participant, or their legally acceptable representative, agreed to participate in a clinical study following completion of the informed consent process. Participants who are assigned to treatment will be considered as Enrolled participants.

Intervention Groups and Duration: All the enrolled participants will be administered Belimumab (10 mg/kg) intravenously over a minimum of 1 hour on Days 0, 14, 28 and then every 28 days through the Week 48 (Day 336) visit.

Safety Review Team (SRT): An internal GSK Safety Review Team will monitor and perform in-stream review of safety data throughout the study.

1.1.1. Schema



Note: Belimumab (10 mg/kg) will be administered intravenously
* - Blood will be collected for pharmacokinetic analysis
# - Participants will remain under clinical supervision for 3 hours after completion of belimumab infusion
x - No belimumab dosing at V3 (Wk1)
BEL-Belimumab, F/up-Follow-up, IV-Intravenous, Scr-Screening, V-Visit, Wk/Wks-Week/s

1.2. Schedule of Activities (SoA)

Procedure	**Screening**	**Observational Period (52 Weeks)**																
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**
Study Day	**up to -35 days**	Day 0	Day 7 ±1 day	Day 14 ±3 days	Day 28 ±3 days	Day 56 ±7 days	Day 84 ±7 days	Day 112 ±7 days	Day 140 ±7 days	Day 168 ±7 days	Day 196 ±7 days	Day 224 ±7 days	Day 252 ±7 days	Day 280 ±7 days	Day 308 ±7 days	Day 336 ±7 days	Day 364 or **Exit** (4 weeks post last dose)[1] ±7 days	16 Week post last dose Follow-Up[9] ±7 days
Study Week		**Wk 0**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk52 / EW**	
Informed consent	X																	
Inclusion and exclusion criteria	X																	
Demography	X																	
Medical history	X																	
Safety Assessments																		
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Symptom Driven Physical Exam	X[7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Daily Prednisone Dose	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight +Height [2]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG	X																	
Chest X-ray	X																	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																		
Haematology	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	**Screening**	**Observational Period (52 Weeks)**																
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**
Study Day	**up to -35 days**	Day 0	Day 7 ±1 day	Day 14 ±3 days	Day 28 ±3 days	Day 56 ±7 days	Day 84 ±7 days	Day 112 ±7 days	Day 140 ±7 days	Day 168 ±7 days	Day 196 ±7 days	Day 224 ±7 days	Day 252 ±7 days	Day 280 ±7 days	Day 308 ±7 days	Day 336 ±7 days	Day 364 or **Exit** (4 weeks post last dose)[1] ±7 days	16 Week post last dose Follow-Up[9] ±7 days
Study Week		**Wk 0**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk52 / EW**	
Urinalysis[3]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spot Urine (protein to creatinine ratio)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test[4, 8]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																		
CCI																		
ANA	X																	
CCI																		
HIV, Hepatitis B and C screening	X																	
QuantiFERON-TB Gold Plus	X																X	
PT, PTT	X																	
Efficacy Assessment																		
SELENA SLEDAI	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
SLE Flare Index	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
PGA	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Parent GA	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Treatment																		
Belimumab administration		X[6]		X[6]	X	X	X	X	X	X	X	X	X	X	X	X		
PK Sampling [5]		X	X[10]	X[11]			X[12]											

ANA- Anti-nuclear antibody, CCI [redacted], ECG- electrocardiogram, EW- Early withdrawal, CCI [redacted] PT- Prothrombin time, PTT- Partial thromboplastin time, SELENA SLEDAI- Safety of Estrogen in Lupus National Assessment - Systemic Lupus Erythematosus Disease Activity Index, Wk- Week

1. The Exit visit (Day 364) will occur approximately 4 weeks after the last dose of belimumab. For participants who withdraw from treatment prior to Week 48, in addition to the 16-week follow-up visit and assessments, an EW visit should be completed. The EW visit requires identical assessments and procedures to the Week 52 visit.
2. The participant's weight at the current visit should be used for calculating the dose to be administered.
3. Urinalysis includes routine analysis and urinary sediments. At screening, it will also include analysis of drug and alcohol presence.
4. Serum pregnancy test required at screening for all females of childbearing potential. Urine pregnancy test is sufficient for all subsequent visits. A home urine pregnancy test will be provided to all female participants of childbearing potential.
5. Only for participants (approximately 25) from whom PK samples will be collected at Day 0 (0-4 hours after the end of infusion), Day 7 and Day 14 (pre-infusion) and Day 84 (before the start of infusion and 0-4 hours after the end of infusion).
6. Participants will remain under clinical supervision for 3 hours after completion of belimumab infusion
7. Complete physical examination will be done during the visit.
8. For female participants who are not women of childbearing potential (WOCBP) at the screening but become WOCBP during the study, the investigator will confirm the WOCBP status of female participants during each visit and start with pregnancy testing from that visit onwards.
9. The 16-week follow-up requires a phone call to collect AEs and the results of home urine pregnancy test (if applicable) for female participants. The 16-week follow-up may be performed at a clinic visit per local requirement. If the participant transfers into study 217091, 16-week follow-up visit will not be conducted.
10. If miss the sample collection on visit 3, the PK sampling should be rescheduled to any feasible visit at 7 days after dosing with ±3 days window.
11. If miss the sample collection on visit 4, the PK sampling should be rescheduled to any feasible visit at 14 days after dosing with ±7 days window.
12. If miss the sample collection on visit 7, the PK sampling should be rescheduled to when patients take the next dose.

2. INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterised by autoantibody production and abnormal B lymphocyte function. This disorder shares the same aetiology, pathogenesis and diagnosis criteria in paediatric and adult patients [Stichweh, 2004; Thakral, 2016]. Belimumab (also known as LymphoStat-B; BENLYSTA™) is a B-lymphocyte stimulator (BLyS)-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells.

Belimumab (BENLYSTA™) for intravenous (IV) use was approved in the USA in 2011 as an add-on treatment for adult patients with autoantibody positive SLE despite standard therapy. Belimumab IV was approved by the China National Medical Products Administration to treat adult patients with active SLE on 12 July 2019. Results from a phase 2 study (BEL110455) with belimumab in paediatric SLE patients have supported approval of an SLE paediatric indication in children 5-17 years of age in the USA (approval in 26 April 2019), the European Union (approval 21 October 2019) and Japan (20 September 2019).

2.1. Study Rationale

The treatment strategy and medications for SLE are similar between adults (including Chinese) and paediatric patients [Stichweh, 2004; Thakral, 2016]. The existing data of belimumab in Western children (age 5-17 years), adults from Western and northeast Asia allow extrapolation of efficacy to Chinese paediatric patients at the approved dose of 10 mg/kg IV, leading to waiver of phase 3 clinical trial in Chinese paediatric population.

However, there is an absence of information on the safety and efficacy profile of Belimumab in Chinese paediatric SLE patients. The differences between China and Western countries in population density, environment and endemic pathogens may influence the infection rate and safety profile of belimumab in Chinese paediatric population. In addition, the pharmacokinetic profile of belimumab should be further investigated to demonstrate if exposure in Chinese paediatric SLE patients is similar to SLE paediatric patients in Western countries.

Based on a requirement from China's Centre for Drug Evaluation (CDE), GlaxoSmithKline intends to conduct a post approval commitment (PAC) study in Chinese paediatric patients. The objective of this study is to evaluate safety and efficacy of belimumab IV plus background standard therapy in Chinese paediatric patients with active SLE aged 5 to 17 years, and to characterise the pharmacokinetic profile in a subset of the study population.

2.2. Background

The safety profile of belimumab is consistent between the Western adult studies (HGS1006-C1056, HGS1006-C1057, LBSL02; also referred to as the IV Controlled Repeat Dose [CRD] studies) and the North East Asian adult studies (BEL113750). BEL 113750 was a Phase 3, multi-centre, randomised, double-blind, placebo-controlled study, consisting of a 52-week blinded period in Northeast Asia, followed by an open-label

extension period in China to evaluate the efficacy and safety. Also, consistency was also demonstrated between paediatric and adult studies safety results.

2.2.1. Safety of Belimumab

The safety of belimumab in paediatric subjects has been evaluated in one placebo-controlled study, BEL114055.

In the double-blind phase of study BEL114055, 82.5% of subjects experienced at least 1 AE in placebo group and 79.2% in the belimumab 10 mg/kg group. 35.0% of subjects experienced at least 1 SAE in placebo group and 17.0% in the belimumab group. The SOC with the highest incidence of SAEs was infections and infestations (12.5%, placebo; 7.5%, belimumab). Adverse events of special interest in this protocol were death, malignancies, infusion and hypersensitivity reactions, infections, and suicidality. The overall incidence of all infections of special interest was 7.5% in the placebo group and 13.2% in the belimumab group. The incidences of all serious infections of special interest (2.5% placebo, 1.9% belimumab) and all serious opportunistic infections per GSK adjudication (0% placebo, 1.9% belimumab) were similar between treatment groups. No subjects in either treatment group experienced a malignancy AESI. The incidence of depression/suicide/self-injury AESI was 10.0% in the placebo group and 1.9% in the belimumab 10 mg/kg group. One (2.5%) subject in the placebo group experienced a fatal SAE (pancreatitis acute), while no death occurred in the belimumab group.

The safety results in adult study in Northeast Asia including patients from China (BEL113750) and the Western pivotal studies population (1C056 and C1057) are comparable with the paediatric study (BEL114055) presented above. Therefore, it may be estimated that a comparable safety profile would be expected in paediatric patients from China.

2.2.2. Efficacy of Belimumab

There were comparable efficacy results found in the adult study in Northeast Asia including patients from China (BEL113750), the pivotal studies in Western population (C1056 and C1057), and the paediatric study (BEL114055). Therefore, a comparable efficacy would be expected in paediatric patients from China.

The SLE Responder Index (SRI) Response rate at Week 52 for belimumab versus placebo was analysed post-hoc for the subgroup of race. The SRI response rates and observed differences between belimumab versus placebo were generally consistent within the racial groups, although the small number of subjects in the subgroups limits interpretation of these results. The odds of being an SRI responder at Week 52 versus placebo favoured belimumab in all cases, with a range of odds ratio (OR) 1.32 in White subjects (95% CI: 0.42, 4.18) to OR 1.67 in Asian subjects (95% CI: 0.11, 24.25). These results in the Asian subgroup are also consistent with the observed differences in overall study population that had a percentage of SRI responders of 52.8% for the belimumab group compared with 43.6% for the placebo group, an observed difference of 9.24% and OR of 1.49.

2.2.3. Pharmacokinetics of Belimumab

The Pharmacokinetics of IV belimumab (dose ranging from 1 to 20 mg/kg) has been extensively studied in adults with SLE studies (Phase 1, Phase 2, and Phase 3). The PK has been studied in a smaller paediatric population (study BEL114055) and in Chinese adults (study BEL113750). Population PK analyses have been conducted in both adults (Report No. HGS1006-POPPK) and paediatrics (BEL114055 POPPK). Steady-state geometric mean Cmax, Cmin, Cavg, and AUC values were, respectively, 315 µg/mL, 50 µg/mL, 108 µg/mL, and 3012 day.µg/mL in the overall paediatric population; 305 µg/mL, 42 µg/mL, 92 µg/mL, and 2569 day.µg/mL in the 5-11-year-old group, and 317 µg/mL, 52 µg/mL, 112 µg/mL, and 3126 day.µg/mL in the 12-17-year-old group compared to 311 µg/mL, 46 µg/mL, 100 µg/mL, and 2811 day.µg/mL in adults. The results showed belimumab PK to be dependent on body weight, dose-proportional and time-invariant after IV administration, similar to many monoclonal antibodies targeting soluble ligands. Because of body weight difference between Asian and Caucasian subjects, there is small difference in exposure of belimumab when the same dosing regimens are given. However, no clinically relevant difference in efficacy has been observed.

2.2.4. Pharmacodynamics of IV Belimumab

Similar to results of adult IV [Stohl, 2012] studies, reductions in overall B cells, naive B cells, other B cell subsets, and immunoglobulins were observed following IV belimumab administration in paediatric participants in the double blind phase of BEL114055 [GSK document number 2017N34326_00].

2.3. Benefit/Risk Assessment

Overall, the positive benefit/risk profile of IV belimumab in the BEL114055 paediatric SLE cohort appears consistent with that of adult IV and subcutaneous (SC) study populations. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of belimumab may be found in the current Investigator brochure (IB) [IB, GSK document number 2011N128591_06, 2020] and IB supplement(s) (if applicable) and product label.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product - GSK1550188/belimumab		
Infections		
As with other immunomodulators, the mechanism of action of belimumab, which results in a reduction in B-cells and IgG, may increase risk for the development of infections including severe infections, opportunistic infections and Progressive multifocal leukoencephalopathy (PML). Fatal infections have been reported in SLE patients receiving immunosuppressant therapy, including belimumab.	The rate of serious infections for SLE is ~5% of participants receiving either belimumab or placebo.	Exclusions (see Section 5.2) based on history of primary immunodeficiency, CC deficiency CCI level <10 mg/dL), acute or chronic infections requiring management, serologic evidence of Hepatitis B, Hepatitis C or HIV infection, and grade 3 (or greater) hypo gammaglobulinemia or (if unrelated to SLE) grade 3 (or greater) neutropenia, lymphopenia, leukopenia will be applied. Participants whose IgG level falls below 250 mg/dL will have belimumab treatment withheld (See Section 8.3.1 Clinical Laboratory Assessments), and the appropriateness to continue dosing must be discussed and agreed with the Medical Monitor before the next dose. Any participant whose IgG level falls below 250 mg/dL and is associated with a severe or serious infection will have study agent permanently discontinued. A diagnosis of PML should be considered in any participant presenting with new-onset or deteriorating neurological signs and symptoms. The participant should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, discontinuation of belimumab should be considered. If PML is suspected, this should be reported to the Medical Monitor within 24 hours. The appropriateness of continuing belimumab dosing while the case is being assessed, should be discussed.
Infusion-Related reactions, Hypersensitivity Reactions and Immunogenicity		
Administration of belimumab may result in infusion-related systemic reactions and allergic/hypersensitivity reactions.	Administration of belimumab may result in infusion and hypersensitivity reactions, which can be severe and can be fatal. Delay in the onset of serious hypersensitivity reactions can occur. Belimumab has been associated with delayed type non-acute hypersensitivity reaction (HSR)/serum sickness, although	Participants with a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins, or monoclonal antibodies will be excluded from this study. Participants will remain under clinical supervision for 3 hours after completion of the first 2 belimumab infusions. Participants will be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	no relationship to anti-drug antibody (ADA) has been established. Infusion-related systemic reactions and hypersensitivity reactions occur more frequently with the first two doses and tend to decrease with subsequent doses.	attention. Patients will be given an alert card for hypersensitivity/allergic reactions.
Malignancy		
As with other immunomodulating agents, the mechanism of action of belimumab may increase the potential risk for the development of malignancies.	Immunomodulatory drugs like belimumab may increase the risk of malignancy. To date, no causal relationship between belimumab and malignancy, including B cell lymphoma, has been detected.	Participants with a history of malignancy in the 5 years prior to screening will be excluded. Monitor patients for signs and symptoms of malignancy, monitor laboratory values, request that patients report signs and symptoms. Treat appropriately.
Interactions with Vaccinations		
Because of its mechanism of action, belimumab may interfere with the response to immunisations.	The efficacy of concurrent vaccination in patients receiving belimumab is not known; however, in the belimumab vaccination trial, evaluation of the impact of belimumab treatment on response to on-treatment vaccination with 23-valent pneumococcal vaccine revealed that immune responses to the different serotypes were similar in SLE patients receiving belimumab compared with those not receiving treatment at the time of vaccination.	Immunisation with live or live attenuated vaccines is prohibited from 30 days prior to Day 0 and during belimumab use. Participants' vaccination status should be assessed and current immunisation guidelines followed; all necessary vaccinations should be administered no later than 30 days prior to Day 0.
Psychiatric Events		
Psychiatric events including depression and suicidality.	In a recent one-year, randomised, double-blind, placebo-controlled post marketing study (BEL115467) of 4,003 subjects with SLE (1:1 randomisation): Serious adverse events (SAE) of suicidal ideation or behaviour or self-injury were	Participants who, in the investigator's opinion, pose a significant suicide risk will be excluded. Monitor participants for psychiatric signs and symptoms, request that patients report psychiatric symptoms. Treat psychiatric symptoms immediately and appropriately.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	reported in 0.7% (n= 15) of subjects receiving belimumab intravenously 10 mg/kg (IV) vs. 0.2% (n=5) of subjects taking placebo. No suicide-related deaths were reported. SAEs of depression were reported in 0.3% (n=7) of subjects receiving belimumab 10 mg/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 10 mg/kg IV reported suicidal ideation or behaviour and 2.0% (n=39) subjects on placebo reported suicidal ideation or behaviour.	
Hypotension		
Risk of hypotension associated with hypersensitivity reaction.	Hypotension may accompany infusion/post-injection systemic reactions with belimumab. This has rarely been observed in clinical studies with belimumab.	Consider withholding anti-hypertensive medications 12 hours prior to belimumab.

2.3.2. Benefit Assessment

The primary data supporting efficacy of IV belimumab in adults are the Phase 3 trials (C1056 and C1057) in which 1684 participants were treated for up to 52 weeks (C1057) or 76 weeks (C1056) [Furie, 2011; Navarra, 2011]. Belimumab produced significant improvements in the SRI as well as in the individual component SELENA-SLEDAI score in both studies. Pooled analyses demonstrated steroid sparing and decreased risk of severe flares over 52 weeks. Data from completed belimumab clinical studies provided in the current IB and IB supplement(s) (if applicable) since approval continue to show efficacy in the treatment of SLE through decreased SLE flares and decreased disease activity across multiple organ systems. Similar results in adults were observed in the pivotal Phase 3 trial of belimumab SC 200 mg/week [Stohl, 2017], with significant improvements in the SRI and time to first severe flare endpoints. Overall efficacy of IV belimumab in a randomised placebo-controlled clinical trial in paediatric patients with SLE (BEL114055) was consistent with that seen in adult patients.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures that will be implemented to minimise risk to patients participating in this study, the potential risks associated with administration of belimumab are justified by the anticipated benefits that may be afforded to paediatric patients with SLE who choose to participate in this trial.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	**Primary**
➢ To evaluate the safety and efficacy of belimumab IV in Chinese paediatric patients with SLE.	Safety ➢ Incidence of adverse events of special interest (AESIs) through 52 weeks: • All infections of special interest, including serious infections of special interest and opportunistic infections • Infusion-related systemic reactions and anaphylactic reactions • Depression, suicidality • Malignancies Efficacy ➢ Incidence of patients with ≥4-point reduction from Baseline to Week 52 in SELENA SLEDAI

Objectives	Endpoints
Secondary	**Secondary**
➢ To evaluate safety and tolerability of belimumab IV in Chinese paediatric patients with SLE	➢ Incidence of AEs through 52 Weeks ➢ Incidence of SAEs through 52 weeks
➢ To evaluate the efficacy of belimumab IV in Chinese paediatric patients with SLE	➢ Incidence of patients with ≥4-point reduction from Baseline in SELENA SLEDAI by visit ➢ Change from Baseline to Week 52 in Physician Global Assessment (PGA) ➢ Change from Baseline to Week 52 in Parent Global Assessment (ParentGA) ➢ Change from Baseline in daily prednisone equivalent dose at Week 52 ➢ Time to first flare/ first severe flare over 52 weeks
➢ To evaluate the pharmacokinetics of belimumab (10 mg/kg) IV in Chinese paediatric patients with SLE	➢ Median belimumab concentration levels at Day 0, 7 and 14 days post first dose, and pre-infusion and post-infusion at Day 84 ➢ The PK will be evaluated with respect to clearance, volume of distribution and half-life, and individual steady state exposures Cmin, Cavg, Cmax and AUC.
Other	**Other**
CCI [redacted]	

AESI- adverse events of special interest, AUC- Area under the concentration curve, Cmin- the minimum blood plasma concentration reached by a drug prior to administration of a second dose, Cavg- average plasma concentration, IV- Intravenous, ParentGA - Parent Global Assessment, PGA- Physician Global Assessment, SELENA SLEDAI- Safety of Estrogen in Lupus National Assessment - Systemic Lupus Erythematosus Disease Activity Index

4. STUDY DESIGN

4.1. Overall Design

This is a multicentre, single arm, prospective, 52-week study to collect and assess the safety and efficacy of belimumab IV administered in combination with background standard therapy in 65 paediatric participants aged 5 to 17 years with active SLE. The pharmacokinetic profile of belimumab will be investigated in a subset of participants.

Paediatric participants with SLE as diagnosed with American College of Rheumatology (ACR) classification criteria who have active disease (defined as SELENA SLEDAI

score ≥8) at screening will be enrolled. Participants need to be on stable standard SLE therapy for at least 30 days prior to Baseline.

Belimumab (10 mg/kg) will be administered intravenously over a minimum of 1 hour on Days 0, 14, 28, and then every 28 days through the Week 48 (Day 336) visit. All participants will continue to receive their standard SLE therapy with restrictions on the changes that are permitted throughout the 52-week observational period. Participants completed the last Benlysta IV administration at Week 48 and transfer to study 217091 successfully will continue to complete the 52-week visit of 213560. However, 16-week follow-up visit will not be conducted.

Participants may withdraw or discontinue from the study at any time for any reason. Participants withdrawing from belimumab treatment will return for an exit visit, i.e. 4 weeks after their last dose of belimumab, and then continue safety monitoring at the scheduled visit (Section 1.2) until Day 364 if they are willing to stay in safety monitoring. Participants choosing to discontinue from the study and not willing to continue for safety monitoring will return for Exit visit following their last dose of belimumab for safety monitoring.

Participants who complete this study and who are willing to continue belimumab IV treatment with commercially available BENLYSTA™ may participate in an ongoing Intensive Drug Monitoring study of belimumab (Study 213210).

4.2. Scientific Rationale for Study Design

Recent and past studies consistently show that adult and paediatric SLE patients have increased serum B-lymphocyte stimulator (BLyS) levels [Cheema, 2001; Hong, 2009; Petri, 2008; Wang, 2008]. In SLE, the elevation of BLyS may contribute to the persistence of B-cell subsets that produce pathogenic autoantibodies or promote inflammation that would otherwise be prone to down regulation. Thus, a therapeutic strategy that involves an antagonist to BLyS may have therapeutic benefit in SLE. In addition, this therapeutic strategy of utilising a BLyS specific inhibitor, belimumab, proved successful with the positive results from 4 pivotal adult lupus studies. In general, paediatric SLE patients have more severe disease and thus higher disease activity index on an average than adults. Adult SLE patients who presented with disease that is more active performed better with belimumab. Based on this information, it is hypothesised, that belimumab will have a beneficial effect in the paediatric SLE population.

Results of phase 2 study (BEL110455) of belimumab in 93 paediatric SLE patients demonstrated similar efficacy and safety profile in paediatric and adult Western population. Belimumab was granted approval in the United states (US)/Japan/European Union (EU) in 2019 to extend the indication to paediatric patients aged 5 to 17 years with active SLE despite standard therapy.

The existing data thus allow extrapolation from Western paediatrics to Chinese paediatric patients at the approved dose of 10 mg/kg IV and a waiver of phase 3 clinical trial in Chinese paediatric population. However, there is an absence of safety and efficacy profile in Chinese paediatric SLE patients. Overall consistent steady-state average concentrations (Cavg_ss) were predicted in Chinese paediatric patients and Western/Chinese adults

based on a population PK analysis (GSK document number 2020N427517_00). However, the PK exposure of belimumab is to be further confirmed in Chinese paediatric SLE patients. To support the registration of paediatric SLE indication in China, PAC will be conducted to demonstrate that belimumab exposure, efficacy and safety observed in Western paediatric population is similar to that observed in Chinese and Western adults.

The primary objective of this study is to evaluate the safety and efficacy of belimumab in Chinese paediatric patients aged 5 to 17 years with active SLE despite standard therapy. Primary safety endpoint is the occurrence of AESI. Primary efficacy endpoint defined as incidence of patients with ≥4-point reduction from Baseline to Week 52 in SELENA SLEDAI score. Secondary safety endpoint is occurrence of AEs and SAEs. Secondary efficacy endpoints include incidence of patients with ≥4-point reduction in SELENA SLEDAI score from Baseline to Week 52 by visit, Physician global assessment (PGA), parent global assessment (ParentGA), change in daily prednisone dose and SLE flare index. CCI [redacted]

This study will collect the pharmacokinetic samples of belimumab to demonstrate if exposure in a subset (approximately 25) of Chinese paediatric patients with SLE is similar to Western paediatric patients with SLE. Summary statistics including median belimumab concentration levels at Day 0, Day 7, Day 14 and Day 84 (Week 12) will be calculated. The feasibility of this will largely depend on data availability, although efforts will be made to collect as much information as possible. The subsequent data analysis ranges from summary statistics at sampling times to a modelling and simulation analysis after data pooling with other study data. If needed, results of the analysis and comparison with other studies (e.g., BEL110455) will be reported in a separate document.

4.2.1. Participant Input into Design

Not Applicable

4.3. Justification for Dose

Intravenous administration of belimumab 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter has been approved in Western and Chinese adults and in paediatric patients in the US, the EU and Japan. From the prediction based on population PK model, in Chinese pediatric patients with SLE, belimumab 10 mg/kg IV Q4W is expected to have exposure similar to that in Chinese adults and non-Chinese pediatric patients with SLE, supporting the use of this regimen in Chinese pediatric patients with SLE (GSK document number 2020N427517_00). The study will therefore adopt the same dosing regimen.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study up to and including the Week 52 visit.

The end of the study is defined as the date of the last assessment (16-week post-treatment follow-up) of the last participant in the study. For participants switch to study 217091, the end of the study defined as completed Week 52 visit.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Type of Participant and Disease Characteristics

1. Participants have or have had in series, 4 or more of the American College of Rheumatology (ACR) 11 criteria for the classification of SLE (Section 10.7: Appendix 7).
2. Participant's age is 5 to 17 years at the time of informed consent.
3. Have active SLE disease defined as a SELENA SLEDAI score ≥8 at screening (SELENA SLEDAI scoring see Section 10.8: Appendix 8).
4. Have unequivocally positive autoantibody test results defined as an ANA titre ≥1:80 and/or a positive CCI serum antibody test.
5. Are on a stable SLE therapy at Baseline.

   The stable treatment at Baseline consists of corticosteroids, anti-malarials, immunosuppressive/immunomodulatory agents and NSAIDs, alone or in combination, at a fixed dose for a period of at least 30 days prior to Day 0.

   a) Corticosteroids (prednisone or prednisone equivalent up to 0.5 mg/kg/day):

      i. For those participants on alternating day doses of steroids, use the average of 2 daily doses to calculate the average daily steroid dose.

   b) Other immunosuppressive or immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), calcineurin inhibitors (e.g. tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine or thalidomide.

   c) Anti-malarials (e.g. hydroxychloroquine, chloroquine, quinacrine)

   d) Non-steroidal anti-inflammatory drugs (NSAIDs)

   e) New SLE therapy must not be added within 30 days of Day 0.

Sex

6. Male and/or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male Participants

No contraceptive measures are required for male participants.

Female participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP (See Section 10.4, Appendix 4)

  OR

- Is a WOCBP and is using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 (Appendix 4) during the belimumab treatment period and for at least 16 weeks, corresponding to the time needed to eliminate any study intervention(s) (e.g., 5 terminal half-lives), after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

A WOCBP must undergo a negative highly sensitive [Section 10.2, Appendix 2] pregnancy test (serum or as required by local regulations) within 35 days before the first dose of belimumab.

7. The investigator is responsible for review of medical history, menstrual history and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. The investigator, or a person designated by the investigator, will obtain written informed assent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian and the participant’s assent, when applicable, before any study-specific activity is performed. The investigator will retain the original copy of each participant's signed assent document.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Have an estimated glomerular filtration rate (eGFR) as calculated by Schwartz Formula of less than 30 mL/min.
2. Have acute severe nephritis defined as a significant worsening of renal disease (e.g., the presence of urinary sediments and other lab abnormalities) that, in the opinion of the study investigator, may lead to the participant requiring induction therapy with IV cyclophosphamide, MMF or high dose corticosteroids during the first 6 months of the study.

Note: Clinically stable lupus nephritis that can be managed with medications allowed in the study will not exclude participants from participating in the trial (nor will any maximum level of proteinuria exclude participants). Clinical assessment and medical management of nephritis will be at the discretion of the study investigator.

3. Have a history of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
4. Have clinical evidence of significant, unstable or uncontrolled, acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, haematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases) which, in the opinion of the investigator, could confound the results of the study or put the participant at undue risk.
5. Have a planned surgical procedure or a history of any other medical disease (e.g., cardiopulmonary), laboratory abnormality, or condition (e.g., poor venous access) that, in the opinion of the investigator, makes the participant unsuitable for the study.
6. Have a history of malignant neoplasm within the last 5 years.
7. Have a history of a primary immunodeficiency.
8. Have an [redacted] deficiency ([redacted] level <10 mg/dL).
9. Have acute or chronic infections requiring management, as follows:
    a) Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).

    b) Hospitalisation for treatment of infection within 60 days of Day 0.
10. Have recent infections that, in the opinions of the investigator, makes the participant unsuitable for the study or could put the participant at undue risk.
11. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 0.
12. Have a Grade 3 or greater laboratory abnormality based on the protocol toxicity scale (Section 10.2.1) except for the following that are allowed:

a) Stable Grade 3 prothrombin time (PT) secondary to warfarin treatment.

b) Stable Grade 3 partial thromboplastin time (PTT) due to lupus anticoagulant and not related to liver disease or anti-coagulant therapy.

c) Stable Grade 3 hypoalbuminemia due to lupus nephritis and not related to liver disease or malnutrition.

d) Any grade proteinuria

e) Stable Grade 3 gamma glutamyl transferase (GGT) elevation due to lupus hepatitis and not related to alcoholic liver disease, uncontrolled diabetes or viral hepatitis. If present, any abnormalities in the ALT and/or AST must be ≤Grade 2.

f) Stable Grade 3 neutropenia; or stable Grade 3 lymphopenia; or stable Grade 3 leukopenia, due to SLE

13. Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
14. Have evidence of serious suicide risk including any history of suicidal behaviour in the last 6 months or who in the investigator's judgment, poses a significant suicide risk.

Prior/Concomitant Therapy

15. Have received treatment with belimumab at any time.
16. Have received any of the following within 364 days of Day 0:

a) Treatment with any B-cell targeted therapy (e.g., rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc)

b) Abatacept

c) A biologic investigational agent

17. Have required 3 or more courses of systemic corticosteroids for concomitant conditions (e.g., asthma, atopic dermatitis) within 90 days of Day 0 (Topical or inhaled steroids are permitted).
18. Have received any of the following within 90 days of Day 0:

a) Anti-Tumour Necrosis Factor (TNF) or anti-IL-6 therapy (e.g., adalimumab, etanercept, infliximab, tocilizumab certolizumab, golimumab)

b) Interleukin-1 receptor antagonist (anakinra)

c) Intravenous immunoglobulin (IVIG)

d) Plasmapheresis

19. Have received any of the following within 30 days of Day 0:
    a) Intravenous (IV) cyclophosphamide
    b) A non-biologic investigational agent (30 days window OR 5 half-lives, whichever is longer)
    c) Any new immunosuppressive/immunomodulatory agent, anti-malarial, NSAID (See Inclusion Criteria #5)
    d) High dose prednisone or equivalent (>1.5 mg/kg/day) or any intramuscular or intravenous steroid injection
    e) Note: New inhaled steroids, intraarticular steroids, and new topical immunosuppressive agents (e.g., eye drops, topical creams) are allowed. Any NSAID use for <1 week is allowed.
20. Have received a live or live-attenuated vaccine within 30 days of Day 0.
21. Have active central nervous system (CNS) lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident [CVA], cerebritis or CNS vasculitis) requiring therapeutic intervention within 60 days of Day 0.
22. Have required renal replacement therapy (e.g. haemodialysis, peritoneal dialysis) within 90 days of Day 0 or be currently on renal replacement therapy

Prior/Concurrent Clinical Study Experience

23. Participation in an interventional clinical study either concurrently or within 6 months of screening. Participation in an observational study may be permitted.

Diagnostic assessments

24. Have a historically positive test or test positive at screening for HIV antibody.
25. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, chest X-rays (posteroanterior) and a positive (not indeterminate) QuantiFERON-TB Gold Plus test.
26. Hepatitis B: Serologic evidence of Hepatitis B (HB) infection defined as Hepatitis B surface antigen positive (HBsAg+) OR Hepatitis B core antibody positive (HBcAb+).
27. Hepatitis C: Positive test for Hepatitis C antibody at screening.

5.3. Lifestyle Considerations

No lifestyle restrictions are required during the course of this study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the investigator's discretion following discussion with the medical monitor. Such participants will be assigned a new participant number and all screening assessments will be repeated.

5.5. Repeat Assessments during the 35 Day Screening Period

Laboratory assessments may be repeated if determined necessary by the investigator, for example: (a) in cases of technical malfunction (e.g., loss of laboratory specimen), (b) in the event of a value close enough to the exclusionary threshold that it may reasonably lie within the degree of variability of the assay; (c) if there is reason to believe the result may be false (e.g. contradicts recent result for the same parameter).

These are repeat assessments and not rescreening events. If the original result was exclusionary and is confirmed by a repeat test, the participant will be excluded.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

ARM Name	Belimumab 10 mg/kg IV
Intervention Name	Belimumab
Type	Biologic
Dose Formulation	Lyophilised cake for reconstitution and dilution in normal saline
Unit Dose Strength(s)	5 mL vial containing 120 mg lyophilised belimumab (80 mg/mL after reconstitution).
Dosage Level(s)	10 mg/kg body weight by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48.
Route of Administration	IV Infusion
Use	Investigational
IMP and NIMP	IMP

Sourcing	Provided by the Sponsor
Packaging and Labelling	Study Intervention will be provided in vial. Each vial will be labelled as required per country requirement.
Current name	The trade name of the investigational product is BENLYSTA™. The generic (USAN/INN) name is belimumab. Another trademarked name LymphoStat-B. The company code numbers for belimumab are HGS1006 and GSK1550188.

Belimumab is a recombinant, human, IgG1λ monoclonal antibody derived by affinity maturation of a parental antibody which itself was derived from screening a phage display library for high affinity binding to BLyS. Belimumab is expressed in the NS0 mouse myeloma cell line. The secreted belimumab is recovered from the growth medium and purified using a series of chromatography and filtration steps.

Belimumab IV will be supplied in sterile, single-use 5 mL vials as a lyophilised formulation for IV use.

Belimumab IV will be administrated at 10 mg/kg body weight by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48. The calculated dose of belimumab to be administered is determined by participant's body weight at each visit. The calculated dose of study intervention to be administered to the participant is determined in milligrams (mg) by the participant's body weight in kilograms (kg) at each visit. The study intervention should be delivered to all participants in 250 mL of saline solution. Alternatively, infusion bags with 100 mL saline solution may be considered providing that the resulting belimumab concentration in the infusion bag does not exceed 4 mg/mL. When the study intervention is administered at a dose of 10 mg/kg, to maintain a belimumab concentration of 4 mg/mL or less, use of the 100 mL bag may only be considered for the participants whose body weight is ≤40 kg.

The reconstituted belimumab will be diluted in 250 mL or 100 mL normal saline for IV infusion. An amount of normal saline, equal to the calculated amount of product to be added, should be removed from the 250 mL or 100 mL infusion bag prior to adding the product. After adding the reconstituted product, gently invert the bag to mix the solution. The prepared study intervention should be infused over 1 hour.

The dose of study intervention administered may not be altered. The rate of infusion may be slowed or interrupted if the participant appears to develop signs of adverse reaction or infusion-associated symptoms. Rate of infusion should not be increased above recommended rate.

Participants should be monitored during all infusions. Participants should remain under clinical supervision for 3 hours after completion of the first 2 infusions.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. The excipients used in the paediatric formulation are safe for administration in the paediatric population participating in the study. Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
3. The investigator, institution or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation and record maintenance (i.e., receipt, reconciliation and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure, notify the monitor, Medical Monitor and/or GSK study contact.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimise Bias: Randomisation and Blinding

This is an open-label study without randomisation and blinding.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the

participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Permitted medications and non-drug therapies

Participants must be on a stable SLE therapy for at least 30 days prior to Day 0. Corticosteroids may be added as new medication or their doses adjusted only up to 30 days prior to Day 0.

Once the participant receives the first dose of belimumab on Day 0, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required; however, changes in certain medications (as outlined below) may result in the participants being withdrawn from the study.

6.5.1.1. Anti-malarials

A new anti-malarial (e.g., hydroxychloroquine, chloroquine, quinacrine) may be started between Day 0 and the 16-week post-treatment follow-up assessment.

The dose of an anti-malarial may be reduced or increased as clinically required, between Day 0 and the 16-week post-treatment follow-up assessment.

An anti-malarial may be replaced by another anti-malarial due to documented toxicity or lack of availability at any time during the study.

6.5.1.2. Steroids

In this section, total systemic steroid dose is defined as the average daily dose of all steroids taken IV, IM, SC, intradermally and orally for both SLE and non-SLE reasons. At Baseline, the average daily dose of steroids is the sum of steroid dose over 7 consecutive days up to, but not including Day 0, divided by 7. While on treatment, the average daily dose of steroids is the sum of steroid dose over any 7 consecutive days divided by 7 in the respective time window.

Systemic Steroids for SLE-related Disease Activity

The total dose of systemic steroids may be increased or decreased as clinically indicated from Day 0 through the 16-week post-treatment follow-up assessment. Treatment of SLE Flares with Steroids: If a participant has an SLE flare requiring an increase in steroid dose the investigator should consider the guidelines prepared for the ACR, for steroid dose/duration of induction therapy [Liang, 2004].

Intra-articular Injections

Participants may receive intraarticular (IA) corticosteroid injections at any time between Day 0 and the 16-week post-treatment follow-up assessment.

Steroids for Reasons Other Than SLE Disease Activity

Inhaled and topical steroids are allowed throughout the course of the study.

Steroids may be given for reasons other than SLE disease activity (such as asthma, contact dermatitis) as clinically indicated.

6.5.1.3. Other Immunosuppressive/Immunomodulatory Agents

Starting any new allowable immunosuppressive/immunomodulatory agent is permitted from Day 0 through the 16-week post-treatment follow-up assessment.

The dose of existing immunosuppressive/immunomodulatory agents may be increased or decreased, as clinically required, from Day 0 through the 16-week post-treatment follow-up assessment.

An immunosuppressive/immunomodulatory agent may be replaced with one of the agents above due to documented toxicity or lack of availability. New topical immunosuppressive agents (e.g., eye drops, topical creams) are allowed from Day 0 through the 16-week post-treatment follow-up visit.

6.5.1.4. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs may be given within 30 days prior to Day 0 only if given for <1 week. From Day 0 through the 16-week post-treatment follow-up visit, NSAIDs may be given as clinically indicated (even if >1 week). An NSAID may be replaced with another NSAID due to documented toxicity or lack of availability.

Anti-thrombotic doses of aspirin are permitted at any time during the study.

Paracetamol (acetaminophen) is primarily an analgesic and lacks the anti-inflammatory properties of other NSAIDs. The use of paracetamol is recommended when possible to treat non-SLE related conditions, in the absence of a pre-existing hepatic function deficiency.

6.5.2. Prohibited Medications and Non-Drug Therapies

Participants who start prohibited medications or therapies at any time during the study will be considered protocol violation. Belimumab will be discontinued and participants will be withdrawn from the study.

The following medications and therapies are prohibited at any time during the study:

- Other investigational agents (biologic or non-biologic). Investigational applies to any drug not approved for sale in the country in which it is being used.

- Participation in a study using an investigational agent or non-drug therapy that may interfere with the conduct of this protocol, except study 217091.
- Anti-TNF or anti-IL-6 therapy (e.g., adalimumab, etanercept, infliximab, certolizumab, tocilizumab, golimumab).
- All biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist).
- Intravenous immunoglobulin (IVIG).
- IV cyclophosphamide (oral cyclophosphamide is permitted).
- Plasmapheresis, leukapheresis.
- Any live or live attenuated vaccines. (Participants who require a live or live attenuated vaccine during the study should have belimumab discontinued prior to receiving the vaccine).

6.6. Dose Modification

No dose modifications of belimumab are allowed.

6.7. Intervention after the End of the Study

Following the end of treatment at Week 48 or early withdrawal from the study, the participant will return to standard of care for SLE as determined by the investigator.

Participants completed the last Benlysta IV administration at Week 48 and transfer to study 217091 successfully will continue to complete the 52-week visit of 213560. However, 16-week follow-up visit will not be conducted.Participants who complete this study and who are willing to continue belimumab IV treatment with commercially available BENLYSTA™ may participate in an ongoing Intensive Drug Monitoring study of belimumab (Study 213210).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will not remain in the study to be evaluated for Safety and efficacy. See the SoA (Section 1.2) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Participants may be withdrawn from belimumab treatment or from this study if at any time:

- Withdrawal of consent by the participant (or their legally acceptable representative) for any reason.

- The investigator judges it necessary due to medical reasons.

Furthermore, participants will be withdrawn from belimumab treatment, if at any time:

- Participant becomes pregnant

- Receives prohibited therapy (Definition see Section 6.5.2)

- Participates in another interventional trial, except study 217091

- Misses 3 or more consecutive belimumab infusions

- Experiences unacceptable toxicity

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology.

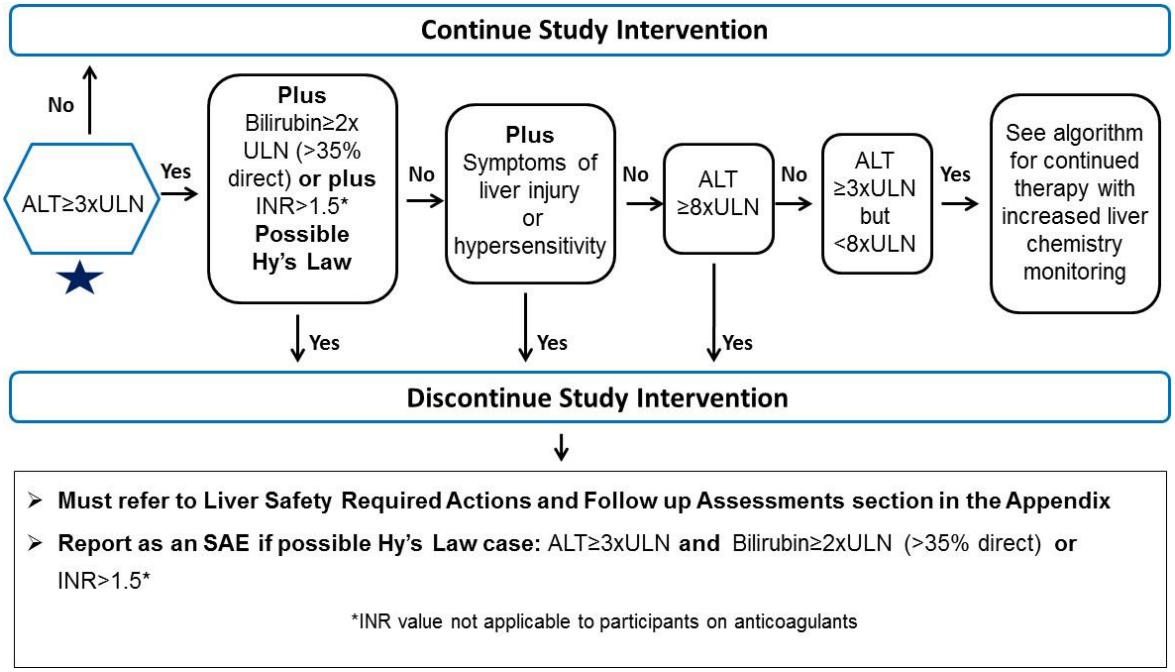
Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined **Algorithm A** or **Algorithm B**

OR

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

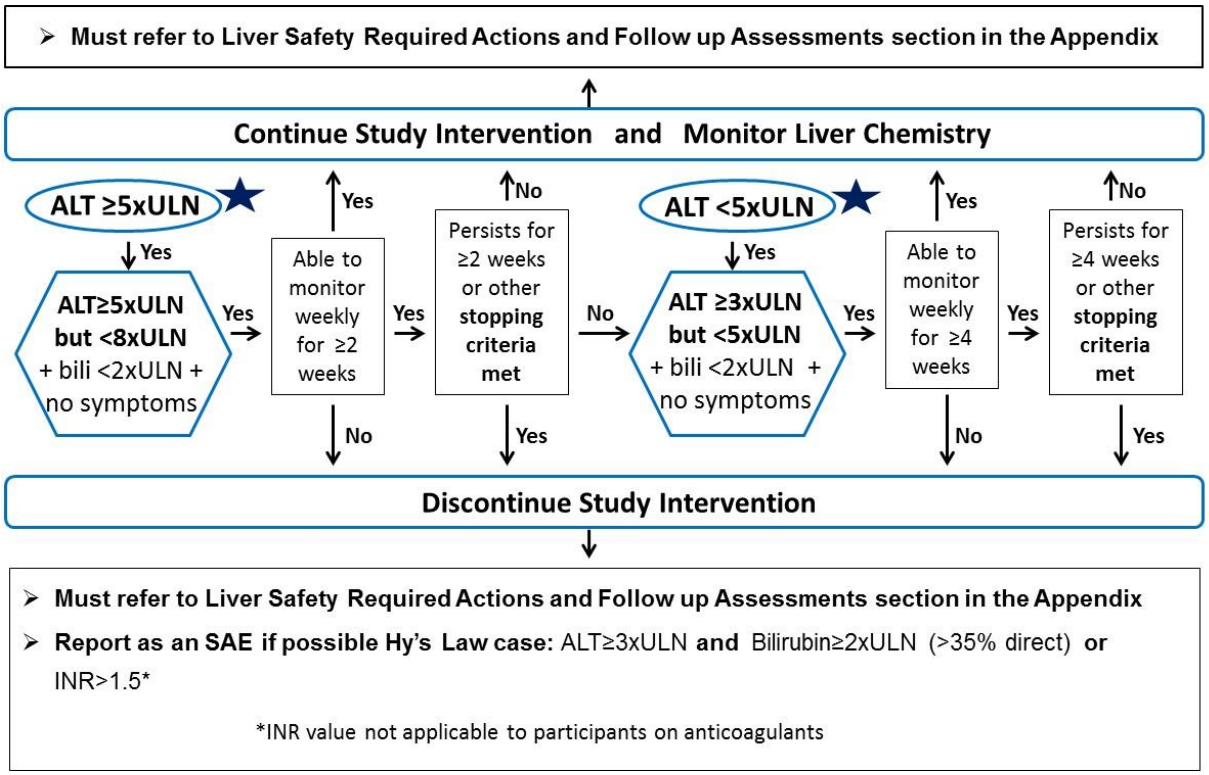
Algorithm A: Phase 3/4 Liver Chemistry Stopping and Increased Monitoring Algorithm



Abbreviations: ALT = alanine transaminase; bili = bilirubin; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Section 10.5 (Appendix 5) for required Liver Safety Actions and Follow-up Assessments

Algorithm B: Phase 3/4 Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Abbreviations: ALT = alanine transaminase; bili = bilirubin; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Section 10.5 (Appendix 5) for required Liver Safety Actions and Follow-up Assessments

7.1.2. IgG Stopping Criteria

Any participant who has a Grade 4 IgG level, by the protocol-defined Adverse Event and Laboratory Value Severity Grade Scale (see Appendix 2, Section 10.2.1), will have dosing with study agent withheld, and the appropriateness to continue study treatment must be discussed with the Medical Monitor before the next dose. Any participant who has a Grade 4 IgG level associated with a severe or serious infection will have study agent discontinued and should complete the follow-up assessments as described in the SoA (Section 1.2).

7.1.3. Rechallenge

7.1.3.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.1.4. Temporary Discontinuation

In the event of a participant experiencing an AE or SAE, the investigator may at their discretion choose to instruct the participant/caregiver to skip one or more scheduled administrations of belimumab. If a participant misses 3 or more consecutive belimumab infusions, participant will be withdrawn from belimumab treatment.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation or exit visit should be conducted, as shown in the SoA (Section 1.2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant's parent/caregiver withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, her/his parent/caregiver may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1 (Appendix 1).

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed local guidelines.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples

8.1. Screening Assessments

Information collected during the screening phase assessments represent key data that identify and define participant Baseline status. This information is critical for evaluation of subsequent safety assessments.

Informed Consent

Informed consent will be obtained from the participant's parent/legally appointed representative (LAR) prior to the initiation of any study procedures or study-specific data collection. The participant will provide their assent to participate in the study at the same time.

After obtaining written informed consent from participant's parent/LAR and assent from participants, the participant will be screened (up to 35 days) for eligibility. A participant

may have treatment assigned when all screening procedures have been completed and eligibility criteria confirmed.

Screening Assessments

During the screening period, the following assessments will be performed:

Demographic parameters will be captured: Date and year of birth, sex, race and ethnicity.

Medical history/medication will be assessed as related to the exclusion criteria listed in Section 5.2. A complete medical history will be taken at the Screening Visit. Information from the medical history is important to establish the Baseline condition of the participant and will impact the safety monitoring assessments during the study. Any significant medical conditions affecting the participant in the past 5 years should be recorded on the Medical conditions page of the eCRF. The history should include the following:

- Confirm classification of SLE disease (based on ACR criteria) by reviewing previously documented clinical records.
- Past or current conditions
- Prior surgical procedures
- Pharmacotherapy and chronic or current use of any medication or herbal preparation
- Allergies and significant allergic reactions
- Significant infections, or history of recurrent infection, including urinary and respiratory tract infections
- Smoking history (current or previous smoker, number of cigarettes smoked per day)

Pregnancy Test

A serum pregnancy test will be performed for females of childbearing potential at the Screening Visit, and a urine pregnancy test will be performed during each subsequent clinic visit. Refer to the pregnancy section (Section 8.4.5).

Investigator will confirm the WOCBP status of female participants during each visit. For females who are not WOCBP at the screening visit, but become WOCBP during the study, pregnancy test will be performed according SoA from that onwards.

Full Physical Examination, Height, Weight and Vital Signs

The full physical examination will include complete assessment of all organ systems including assessments of the head and neck (including eyes, ears, nose, throat, and thyroid gland), skin, musculoskeletal (including evaluation of both small and large joints), neurological, respiratory, and cardiovascular systems, gastrointestinal system, and abdomen (including liver and spleen), lymph nodes and extremities.

Height and weight, and vital signs (systolic and diastolic blood pressure [sitting], heart rate, and body temperature) will be measured and recorded.

Electrocardiogram

A single 12-lead ECG will be obtained for screening purposes only as outlined in the SoA (see Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS and QT intervals. If the screening ECG is abnormal, the Investigator may at their discretion exclude the participant from the study and/or contact the Medical Monitor to discuss the appropriateness of including the participant.

Chest X-ray

A chest X-ray (posteroanterior) will be taken for screening purpose as outlined in the SoA (see Section 1.2).

Laboratory Tests

The following laboratory tests will be performed by the central laboratory at screening, as related to the eligibility criteria described in Section 5.

Blood tests

- Haematology
- Modified Chem 20 (non-fasting) (CPK MUST be done for participants with myositis in order to score SELENA SLEDAI)
- HIV antibody, Hepatitis B surface antigen, anti-HBc, anti-HBs and Hepatitis C antibody testing.
- Prothrombin time (PT), partial thromboplastin time (PTT)
- CCI [redacted]
- CCI [redacted]
- ANA and CCI [redacted]
- QuantiFERON-TB Gold Plus
- NOTE: To maintain the volume of blood collection with local guidelines, the screening assessments for participants <30 kg will be split across 2 visits separated by a minimum of 2 weeks. There must also be a minimum of 2 weeks between the second screening and the Day 0 blood draws (see SRM for details). This may also apply to participants ≥30 kg according to local guidelines.

Urine sample:

- Routine urinalysis
- Spot urine for macroscopic/microscopic/proteinuria assessments
- Urine protein:creatinine ratio

Disease activity scales:

- SELENA SLEDAI
  - At Screening, confirm SLE disease is active, defined as SELENA SLEDAI score ≥8
- Physician's Global Assessment (PGA) (Section 10.10: Appendix 10)
- Parent Global Assessment (ParentGA) (Section 10.11: Appendix 11)
- SLE Flare Index (Section 10.9 Appendix 9)

Suicidality Assessment

Possible suicidal behaviour or ideation will be assessed at screening (See Section 5.2, exclusion #14).

Baseline Assessment

Procedures at the Baseline Visit are listed in the SoA (Section 1.2). They include clinical assessments including efficacy, laboratory tests and biomarkers. The interim medical history, including concomitant medications should be reviewed to ensure the participant's eligibility for the study has not changed.

8.2. Efficacy Assessments

Planned efficacy assessments will be conducted with the following 4 disease activity scales as mentioned in SoA table (Section 1.2): SELENA SLEDAI, PGA, ParentGA and SLE Flare index

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.2).

- A complete physical examination will be included at screening and symptoms driven physical examination at the time points mentioned in the SoA table (Section 1.2).
- Adverse event (including infusion-related and hypersensitivity reactions, infections and malignancies) reported throughout the 52-week treatment period.
- Haematological and clinical chemistry parameters (including urinalysis) throughout the 52-week treatment period.
- Vital signs (i.e., heart rate and systolic and diastolic blood pressure) throughout the 52-week treatment period.
- Additional safety tests (such as vital signs, physical examinations and laboratory safety tests) or change in timing or addition of assessments may be performed during the course of the study based on newly available data to ensure appropriate safety monitoring.

- The possible suicidality related event (PSRAE) form must be completed in the eCRF, if evidence of suicidal behaviour or ideation by a participant is detected at any visit.

8.3.1. Clinical Safety Laboratory Assessments

- Refer to Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.2) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 60 days after the last dose of study intervention should be repeated until the values return to normal or Baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/Baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the SoA.
- Laboratory toxicity will be graded using the Adverse Event and Laboratory Value Severity Grading Table (Section 10.2.1). The Table is based upon publicly available Tables from the National Institute of Allergy and Infectious Disease Division of Microbiology and Infectious Diseases (www.niaid.nih.gov). Lymphopenia will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (U.S. Department of Health and Human Services, 2010).

8.4. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3 (Appendix 3).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the belimumab treatment (see Section 7).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 1.2). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 1.2).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 (Appendix 3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. Non-serious related AEs should be reported using ADR CRF to the sponsor pharmacovigilance team (qwy11935@gsk.com) via email within 5 calendar days.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and related AE and non-serious and serious AEs of special interest (AESI) (i.e., post-injection systemic reactions and hypersensitivity reactions, infections, malignancies, and depression/suicidality/self-injury) will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3 (Appendix 3).

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

If a pregnancy in a female participant is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4 (Appendix 4).

A pregnancy is not considered to be an SAE, although abnormal pregnancy outcomes or complications (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.

There is no requirement to collect pregnancy information from female partners of male participants.

8.5. Treatment of Overdose

There is limited experience with overdosage of belimumab. Adverse reactions reported in association with cases of overdosage have been consistent with those expected for belimumab.

Two doses up to 20 mg/kg administered 21 days apart by IV infusion have been given to humans with no increase in incidence or severity of adverse reactions compared with doses of 1, 4 or 10 mg/kg.

GSK does not recommend specific treatment for an overdose of belimumab.

In the event of a belimumab overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdosing.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics

Blood samples will be collected for measurement of serum belimumab concentrations according to schedules that depend on the paediatric cohort.

Table 1 PK visit days and sample times study participants

Day (Week)	Time (Related to Dosing of Study agent)
0	0-4 hours after the end of infusion
7 (Week 1)	Day 7 ± 1 day
14 (Week 2)	Day 14 ± 3 days (Before the start of infusion)
84 (Week 12)	Day 84 ± 7 days (Before the start of infusion and 0-4 hours after the end of infusion)

On days belimumab is administered and blood samples for pharmacokinetic analysis are obtained, participants may have an intravenous cannula inserted in the contralateral arm to the arm in which belimumab is administered for laboratory safety assessments and serial pharmacokinetic sampling. Blood samples for pharmacokinetic analysis should not be taken from the same arm as that used for the administration of belimumab. Samples may be obtained by venepuncture. The actual date and time (24-hour clock time) of each sample will be recorded.

If sampling for PK is missed, the impact will be minimized by attempting to reschedule the missing PK sampling to ensure sufficient precision of PK characterization in Chinese paediatric patients:

- For the scenario that patients will miss the sample collection on visit 3 (Day 7±1 day), the PK sampling should be rescheduled to any feasible visit at 7 days after dosing with ±3 days window.
- For the scenario that patients will miss the sample collection on visit 4 (Day 14±3 days), the PK sampling should be rescheduled to any feasible visit at 14 days after dosing with ±7 days window.
- For the scenario that patients will miss the sample collection on visit 7 (Day84±7 days), the PK sampling should be rescheduled to when patients take the next dose.

Please refer to the Study Reference Manual for PK sample collection, processing and shipping instructions.

CCI

8.8. Genetics

Genetic analysis will not be evaluated in this study.

8.9. Immunogenicity Assessments

The presence of antibodies to belimumab will not be evaluated in this study.

8.10. Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This is an open-label study. A descriptive approach will be used, and no formal inference is planned in this study. For primary efficacy evaluation, using the percentage of participants with ≥4-point reduction from baseline in SELENA SLEDAI at Week 52 in the placebo group in a Phase 2 paediatric study (Study BEL114055) as target value to guide the analysis planned for Chinese PAC study. The target can be described as the observed proportion of patients with clinical benefit >43.6% (the mean placebo group response rate estimate in study BEL114055).

9.2. Sample Size Determination

Focusing on serious infections, the incidence rate of the serious AE “Infections and Infestations” (SOC) was 7.5% (4/53 participants) in the 10 mg/kg-IV group of the global paediatric study (Study BEL114055).

Under the assumption that the incidence rate of the serious infections is 7.5%, it is calculated that a study with 65 participants will have more than 99.0% probability to observe at least one serious infection. Under this sample size, for any other adverse events, there are more than 90% probability to observe at least one event once the incidence rate is larger than 4%. Additionally, using the Exact method in PASS 2019 for the confidence interval (CI) around a single proportion: a sample size of 65 would have produced a 95% CI of [2.4%, 16.8%] when the incidence rate of the serious infections is 7.5%.

For the efficacy purpose, as one of the key efficacy endpoints, the estimated percentage of participants with ≥4-point reduction from Baseline in SELENA SLEDAI at Week 52 is 54.7% in BEL114055. Using the Exact method in PASS 2019 for the confidence interval (CI) around a single proportion: a sample size of 65 would produce a 95% CI of [41.9%, 67.1%] when the estimate is 54.7%. Under the assumption that the percentage of participants with ≥4 points reduction from baseline in SELENA SLEDAI at week 52 is 54.7%, it is calculated by simulation that a study with 65 participants will have more than 95.0% probability to observe a percentage lager than 43.6%.

9.2.1. PK Sample Size Determination

The FDA recommends that for paediatric studies, the 95% confidence interval of the average CL and V estimates are within 60% to 140% of the geometric mean, with at least 80% power [Wang, 2012]. The same principles are applied here, but for this study a more stringent criterion will be applied requiring the precision of the CL and V to be determined within 80% to 120% of the geometric mean with at least 80% power. It is recommended to collect PK blood samples from 25 Chinese paediatric patients, which is considered the minimum number to meet this more stringent condition and therefore enable a quantitative comparison with the PK in a Western paediatric population.

The sampling of the PK from each subject will be sparse, but when the data is integrated with the population PK model previously developed for paediatrics, the belimumab clearance (CL) and volume of distribution (V) may be estimated for each subject as if the PK had been frequently sampled in these subjects. To show that PK samples from N=25 evaluable Chinese paediatric patients should be sufficient to accurately determine the PK in a Chinese paediatric population, one needs to consider the precision of the average CL and V estimates derived from the N=25 individual values.

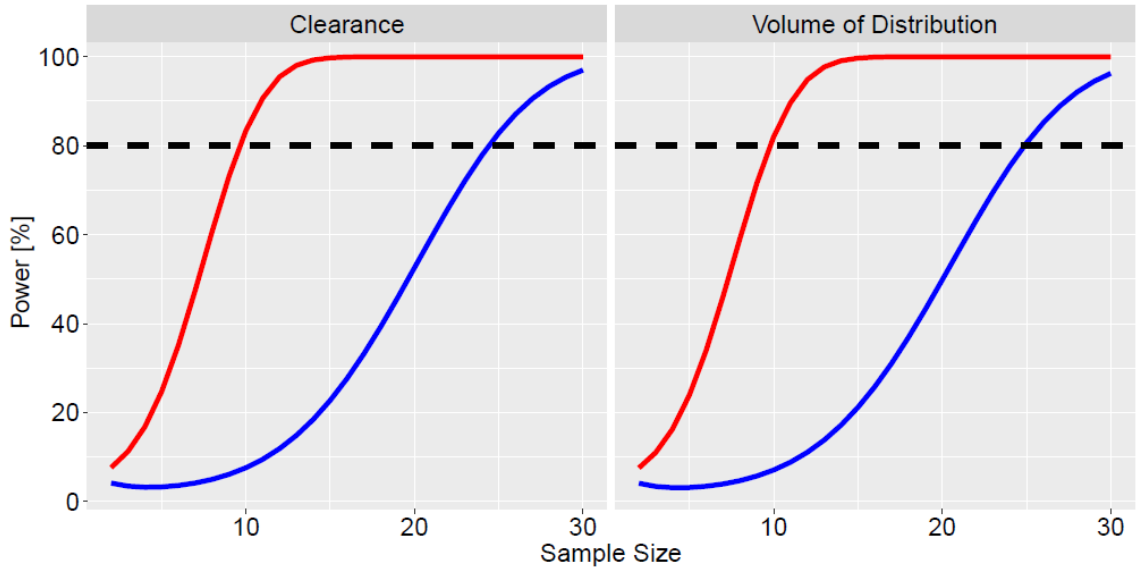
The power to estimate the CL is calculated by integrating over all possible values of the estimated standard deviation *s*, weighted by the probability density and for each value assigning one to the integrand if the 95% confidence interval is within the 80% to 120% range or zero otherwise:

$$Power = \int_0^\infty ds \times f(s; N-1) \times \lambda$$

where $\lambda = \begin{cases} 1 & \text{if } 80\% < CI_{95\%} < 120\% \\ 0 & \text{othewise} \end{cases}$

The results from this power calculation show N=25 paediatric subjects with evaluable PK results in at least 80% power to estimate the CL and V with 95% confidence intervals within 80% to 120% of their geometric mean values (blue line, Figure 1). In this regard the precision of the CL and V estimates in a Chinese paediatric population can be considered sufficient for this study design to compare against the corresponding parameters derived in a Western paediatric population. Additionally, there is 100% power the same sample size will estimate CL and V with 95% confidence intervals within the wider window of 60%-140% of their geometric means (red line, Figure 1).

Figure 1 The power to estimate CL and V versus sample size



The power to estimate the 95% confidence interval within 80% to 120% of the geometric mean is shown (blue solid line). The power calculation was also repeated for the less stringent criteria requiring the 95% confidence interval to be within 60% to 140% of the geometric mean (red solid line).

9.3. Populations for Analyses

Table 2 Definitions of analyses population

Population	Description
Screened	All participants whose parent/caregiver sign the ICF
Enrolled	All participants assigned treatment.
Intent to Treat (ITT)	All participants assigned treatment who received at least one dose of study treatment.

Population	Description
PK	All participants assigned treatment who received at least one dose of study treatment and for whom at least one post belimumab treatment PK sample was obtained and analysed.

9.4. Statistical Analyses

9.4.1. General Considerations

No formal hypothesis testing is planned in the study; all analyses are descriptive.

9.4.1.1. Safety Analysis

All safety analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Primary (Safety)	Endpoints: Incidence of adverse events of special interest (AESIs) through 52 weeks: ○ All infections of special interest, including serious infections of special interest and opportunistic infections ○ Infusion-related systemic reactions and anaphylactic reactions ○ Depression, suicidality ○ Malignancies Analysis: Descriptive statistics will be used to summarise AEs, SAEs and AESIs. The frequency of AEs will be tabulated by MedDRA system organ class (SOC) and preferred term.

9.4.2. Primary Endpoint(s)

9.4.2.1. Efficacy Analysis

All efficacy analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Primary (Efficacy)	Endpoint: Incidence of participants with ≥4-point reduction from Baseline to Week 52 in SELENA SLEDAI

Endpoint	Statistical Analysis Methods
	Analysis: Descriptive statistics with frequency, percentage and 95% CI will be used to summarise incidence of participants with ≥4-point reduction from Baseline to Week 52 in SELENA SLEDAI. Further, the corresponding results of the previous study (BEL114055) will be used to guide the evaluation of consistency for this efficacy endpoint collected on Chinese subjects.

9.4.3. Secondary Endpoint(s)

Endpoint	Statistical Analysis Methods
Secondary	Endpoints: • Incidence of participants with ≥4-point reduction from Baseline in SELENA SLEDAI by visit • Change from Baseline to Week 52 in Physician Global Assessment (PGA) • Change from Baseline to Week 52 in Parent Global Assessment (ParentGA) • Change from Baseline to Week 52 in daily prednisone equivalent dose • Time to first flare/ first severe flare over 52 weeks Analysis: Descriptive statistics with frequency, percentage and 95% CI will be used to summarise the incidence of participants with ≥4-point reduction from Baseline in SELENA SLEDAI by week. Other endpoints will be summarised by descriptive statistics with mean, median, SD and 95% CI.

All pharmacokinetic (PK) analyses will be performed on the PK Population.

Endpoint	Statistical Analysis Methods
Secondary	Endpoints: Median belimumab concentration levels at Day 0, 7 and 14 days post first dose, and pre-infusion and post-infusion at Day 84 Analysis: Descriptive statistics will be used to summarise the observed belimumab concentrations. Pharmacokinetic parameters with respect to clearance, volume

Endpoint	Statistical Analysis Methods
	of distribution and half-life, and individual steady state exposures Cmin, Cavg, Cmax and AUC will be evaluated.

CCI

[redacted]

9.5. Interim Analyses

No formal interim analyses are planned.

9.6. GSK safety review team (SRT)

The study Medical Monitor and members of the GSK SRT will perform in-stream review of all safety data for the duration of the study and make and communicate recommendations as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
    - Reporting cases of suspected child abuse and/or neglect according to local medical association (e.g., AAP) or health department guidelines.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative will be required to provide a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that legally authorised representative (parent/guardian) consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained before the participant was enrolled in the study and the date the written consent was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICF was the participant's legally authorised representative (parent/guardian). The authorised person obtaining the informed consent must also sign the ICF.
- Participants and their legally authorised representative (parent/guardian) must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.
- Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.
- A copy of the ICF(s) must be provided to the participant or the participant's parent/guardian.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the

sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

10.1.8. Study and Site Start and Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

Inadequate recruitment of participants by the investigator

Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally

support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the central laboratory.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals on WOCBP during intervention.
- The investigator will confirm the WOCBP status of female participants during each visit. For females who are not WOCBP at the screening visit, but become WOCBP during the study, pregnancy test will be performed according to the SoA from that visit onwards.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 30 days and correspond with the time frame for female participant contraception in Section 5.1, Inclusion Criteria
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Calcium	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin

Laboratory Assessments	**Parameters**			
	Calcium corrected for Albumin Inorganic Phosphate	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Carbon dioxide	Magnesium	Alkaline phosphatase	Albumin
	Glucose (nonfasting)	Creatine phosphokinase (CPK)	Gamma glutamyl transpeptidase (GGT)	Creatinine
	Uric acid	Blood urea nitrogen (BUN)	BUN/creatinine ratio	Estimated Creatinine Clearance/GFR (Schwartz[3])
Routine Urinalysis	• pH, glucose, protein, blood, ketones, occult blood by dipstick • Microscopic examination			
Urine Pregnancy[2]	• Urine pregnancy if applicable			
CCI [redacted] CCI				
PK	• Blood collection			
CCI [redacted]	• ANA titre, CCI [redacted]			
Other Screening Tests	• Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Highly sensitive human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], anti-HBs Antibody, anti-HBc antibody and hepatitis C virus antibody) • Prothrombin time (PT), Partial thromboplastin time (PTT)			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.2 and Appendix 5. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalised ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. A home kit will be provided to perform urine pregnancy test.
3. Schwartz, 2009

10.2.1. Adverse Event and Laboratory Value Severity Grade Table

HEMATOLOGY	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Haemoglobin	> 9.5 - 11.0 g/dL	> 8.0 – 9.5 g/dL	6.5 - 8.0 g/dL	< 6.5 g/dL
Leukocytes	3000-3999/mm3	2000-2999/mm3	1000-1999/mm3	< 1000/mm3
Absolute Neutrophil Count	1500-1999/mm3	1000-1499/mm3	500-999/mm3	< 500/mm3
Platelets	75,000 - 99,999/mm3	50,000 – 74,999/mm3	25,000 - 49,999/mm3	< 25,000/mm3
Prothrombin Time (PT)	> 1.0-1.25 x ULN*	> 1.25-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0 x ULN
Partial Thromboplastin Time (PTT)	> 1.0-1.66 x ULN	> 1.66-2.33 x ULN	> 2.33-3.0 x ULN	> 3.0 x ULN
Methaemoglobin	5.0-10.0 %	10.1-15.0 %	15.1-20.0 %	> 20%
Lymphocyte count**	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L

(continued)

*ULN = Upper Limit of Normal
**Lymphopenia calculated from CTCAE table

Adverse Event and Laboratory Value Severity Grade Table (continued)

CARDIOVASCULAR	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac Arrhythmia	-	Asymptomatic/transient; dysrhythmia; no treatment req	Recurrent/persistent dysrhythmia. Symptomatic; treatment req	Unstable dysrhythmia hospitalisation and treatment required
Hypotension	Transient orthostatic hypotension, no treatment	Symptoms correctable with oral fluid treatment	IV fluid req, no hospitalisation req	Hospitalisation req
Hypertension	Transient, increase > 20 mm/Hg; no treatment	Recurrent; chronic increase > 20 mm/Hg, treatment req	Acute treatment req; out subject hospitalisation possible	Hospitalisation req
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion, pain, ECG changes	Tamponade OR pericardiocentesis OR surgery req
Haemorrhage, Blood Loss	-	Mildly symptomatic; no treatment required	Gross blood loss OR 1-2 units transfused	Massive blood loss OR > 2 units transfused

(continued)

Adverse Event and Laboratory Value Severity Grade Table (continued)

	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
CHEMISTRIES				
Sodium				
Hyponatremia	130-135 meq/L	123-129 meq/L	116-122 meq/L	< 116 meq/L
Hypernatremia	146-150 meq/L	151-157 meq/L	158-165 meq/L	> 165 meq/L
Potassium				
Hypokalaemia	3.0-3.4 meq/L	2.5-2.9 meq/L	2.0-2.4 meq/L	< 2.0 meq/L
Hyperkalaemia	5.6-6.0 meq/L	6.1-6.5 meq/L	6.6-7.0 meq/L	> 7.0 meq/L
Phosphate				
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL	1.0-1.4 mg/dL	< 1.0 mg/dL
Calcium- (Corrected For Albumin)				
Hypocalcaemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.1-6.9 mg/dL	< 6.1 mg/dL
Hypercalcemia	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	>13.5 mg/dL
Magnesium				
Hypomagnesemia	1.2-1.4 meq/L	0.9-1.1 meq/L	0.6-0.8 meq/L	< 0.6 meq/L
Albumin				
Hypoalbuminemia	3.00-3.49 g/dL	2.50-2.99 g/dL	2.00-2.49 g/dL	< 2.00 g/dL
Bilirubin (Total)				
Hyperbilirubinemia (Total)	> 1.0-1.5 x ULN	> 1.5-2.5 x ULN	> 2.5-5 x ULN	> 5 x ULN
Glucose				
Hypoglycaemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	< 30 mg/dL
Hyperglycaemia (nonfasting & no prior diabetes)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	> 500 mg/dL
Triglycerides	151-399 mg/dL	400-750 mg/dL	751-1200 mg/dL	> 1200 mg/dL
Creatinine	> 1.0-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0-6.0 x ULN	> 6.0 x ULN

Adverse Event and Laboratory Value Severity Grade Table (continued)

	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
CHEMISTRIES (continued)				
Uric Acid				
Hyperuricemia	7.5-10.0 mg/dL	10.1-12.0 mg/dL	12.1-15.0 mg/dL	> 15.0 mg/dL
Liver Transferases (AST, ALT, and GGT)	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10.0 x ULN	> 10.0 x ULN
Alkaline Phosphatase	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10.0 x ULN	> 10.0 x ULN
Pancreatic Enzymes				
Amylase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
Pancreatic amylase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
Lipase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
*Hypoglobulinemia (IgG)**	550-700 mg/dL	400-549 mg/dL	250-399 mg/dL	< 250 mg/dL

(continued)

*[Eibl, 1995; Goldfarb, 2001; Yamani, 2001].

Adverse Event and Laboratory Value Severity Grade Table (continued)

GASTROINTESTINAL	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Nausea	Mild OR transient; reasonable intake maintained	Mod discomfort OR intake decreased for < 3 days	Severe discomfort OR minimal intake for ≥ 3 days	Hospitalisation required
Vomiting	Mild OR transient; 2-3 episodes/day OR mild vomiting lasting < 1 week	Mod OR persistent; 4-5 episodes per day; OR vomiting lasting ≥1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR IV treatment req	Hypotensive shock OR hospitalisation required for IV treatment req
Diarrhoea	Mild or transient; 3-4 loose stools per day OR mild diarrhoea lasting < 1 week	Mod OR persistent; 5-7 loose stools per day or diarrhoea lasting ≥1 week	Bloody diarrhoea; OR orthostatic hypotension OR > 7 loose stools/day OR IV treatment req	Hypotensive shock OR hospitalisation req
Oral Discomfort/Dysphagia	Mild discomfort, no difficulty swallowing	Difficulty swallowing but able to eat and drink	Unable to swallow solids	Unable to drink fluids; IV fluids req
Constipation	Mild	Moderate	Severe	Distention with vomiting

Adverse Event and Laboratory Value Severity Grade Table (continued)

RESPIRATORY	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cough (for aerosol studies)	Transient; no treatment	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough; systemic treatment req	
Bronchospasm Acute	Transient; no treatment; FEV1 70% to < 80% (or peak flow)	treatment req; normalises with bronchodilator; FEV1 50% to < 70% (or peak flow)	No Normalisation with bronchodilator; FEV 25% to < 50% (or peak flow), retractions	Cyanosis; FEV1 < 25% (or peak flow) OR intubated
Dyspnoea	Dyspnoea on exertion	Dyspnoea with normal activity	Dyspnoea at rest	Dyspnoea requiring O2 therapy

URINALYSIS	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Proteinuria				
Dipstick Protein	1 +	2-3 +	4 +	Nephrotic syndrome
Spot Urine: Protein:Creatinine Ratio mg/mg	0.2-1.0	> 1.0-2.0	> 2.0-3.5	> 3.5
24 Hour Urine: Protein	200 mg - 1g loss/day	> 1-2 g loss/day	> 2-3.5 g loss/day	Nephrotic syndrome OR > 3.5 g loss/day
Haematuria	Microscopic only > 3 to < 10 RBC/hpf	Gross, No clots ≥10 RBC/hpf	Gross plus clots OR RBC casts	Obstructive OR transfusion required

RBC = red blood cell; hpf = high power field.

Adverse Event and Laboratory Value Severity Grade Table (continued)

MISCELLANEOUS	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Fever (oral > 12 hours)	37.7-38.5°C or 100.0-101.5°F	38.6-39.5°C OR 101.6-102.9°F	39.6-40.5°C OR 103-105°F	> 40.5°C OR > 105°F
Headache	Mild; No treatment req	Mod; or non-narcotic analgesia treatment	Severe; OR responds to initial narcotic treatment	Intractable; OR requiring repeated narcotic treatment
Allergic Reaction	Pruritus without rash	Localised urticaria	Generalised urticaria angioedema	Anaphylaxis
Cutaneous/Rash/ Dermatitis	Erythema, pruritus rash OR dry desquamation	Diffuse maculopapular OR dry desquamation	Vesiculation OR moist desquamation ulceration	ANY ONE: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req surgery, exfoliative dermatitis
Local Reaction (secondary to parenteral treatment- not vaccination or skin test)	Erythema	Induration < 10 mm OR inflammation OR phlebitis	Induration > 10 mm OR ulceration	Necrosis of skin
Fatigue	Normal activity Reduced < 25%	Normal activity Reduced 25-50%	Normal activity reduced > 50%; cannot work	Unable to care for self

Adverse Event and Laboratory Value Severity Grade Table (continued)

NEUROLOGIC	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuro-cerebellar	Slight incoordination OR dysdiadochokinesia	Intention tremor OR dysmetria OR slurred speech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	Unable to stand
Neuro-psych/ mood		none	Severe mood changes requires medical intervention	Acute psychosis requiring Hospitalisation
Paraesthesia (burning, tingling, etc.)	Mild discomfort; no treatment needed	Mod discomfort non-narcotic analgesia req	Severe discomfort; OR narcotic analgesia req with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia
Neuro-motor	Mild weakness in muscle of feet but able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and mod proximal weakness ie, in hands interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheelchair because of muscle weakness
Neuro-sensory	Mild impairment sensations, (ie, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment mod de-sensation, (ie, of vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical.	Severe impairment (dec or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	Sensory loss involves limbs and trunk

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalisation or prolongation of existing hospitalisation

- In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording
When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information in the CRF. It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the SAE coordinator by telephone. Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper CRF
Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **SAE coordinator**. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. Contacts for SAE reporting can be found in SRM.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Vasectomised partner *Note: Vasectomised partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] oral intravaginal transdermal injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] oral injectable
Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those that inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3. Collection of Pregnancy Information:

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy that is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating will discontinue study intervention and withdrawn from the study.

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase 3-4 liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology

Phase 3/4 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within Baseline (see MONITORING below)
• Do not restart/rechallenge participant with study intervention. Permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments.</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, within 6 weeks after last dose[5]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia</td></tr>
</table>

Liver Chemistry Stopping Criteria	
MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within Baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilise or return to within Baseline	• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5 which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A Immunoglobulin M (IgM) antibody; HBsAg and HBcAb (conduct quantitative Hepatitis B DNA test if positivity for HBsAg and/or HBcAb); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase 3/4 liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within Baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalise or return to within Baseline.

10.6. Appendix 6: Country-specific requirements

Not applicable.

10.7. Appendix 7: American College of Rheumatology (ACR) Criteria for SLE

The ACR Criteria for the Classification of Systemic Lupus Erythematosus*
[Tan, 1982; Hochberg, 1997]

Criterion	Definition
1. Malar "butterfly" rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.
2. Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.
4. Oral ulcers	Oral or nasopharyngeal ulceration usually painless.
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints characterised by tenderness.
6. Serositis	a. Pleuritis (convincing history or pleuritic pain or rub heard by physician or evidence of pleural effusion), *OR* b. Pericarditis (documented by ECG, rub, or evidence or pericardial effusion).
7. Renal disorder	a. Persistent proteinuria (> 0.5 grams/day or > 3 + if quantitation not performed) ***OR*** b. Cellular casts (may be red cell, hemoglobin, granular, tubular, or mixed).
8. Neurologic disorder	a. Seizures (in the absence of offending drugs or known metabolic derangements; ie, uremia, ketoacidosis, or electrolyte imbalance) *OR* b. Psychosis (in the absence of offending drugs or known metabolic derangements; ie, uremia, ketoacidosis, or electrolyte imbalance.
9. Hematologic disorder	a. Haemolytic anemia (with reticulocytosis) ***OR*** b. Leukopenia (< 4000/mm^3 total on 2 or more occasions), *OR* c. Lymphopenia (< 1500/mm^3 on 2 or more occasions), *OR* d. Thrombocytopenia (< 100,000/mm^3 in the absence of offending drugs).
10. Immunologic disorder	a. Anti-DNA (antibody to native DNA in abnormal titer), *OR* b. Anti-Sm (presence of antibody to Sm nuclear antigen), *OR* c. Positive-finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilisation (TPI) or fluorescent treponemal antibody (FTA) absorption test.
11. Antinuclear antibody (ANA)	Abnormal titre of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome.

* The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval or observation.

10.8. Appendix 8: SELENA SLEDAI Disease Assessment Scales

SELENA SLEDAI Score (adapted from [Petri, 2005; Bombardier, 1992]) - Score if descriptor is present at time of visit or in the preceding 10 days.

Wgt.	Descriptor	Definition
8	Seizure	Recent onset (last 10 days). Exclude metabolic, infectious drug cause, or seizure due to past irreversible CNS damage.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganised, or catatonic behaviour. Exclude uraemia and drug causes.
8	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	Visual Disturbance	Retinal and eye changes of SLE. Include cytoid bodies, retinal haemorrhages, serious exudate of haemorrhage in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes.
8	Cranial Nerve Disorder	New onset sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	CVA	New onset of CVA(s). Exclude arteriosclerosis or hypertensive causes.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter haemorrhages, or biopsy or angiogram proof of vasculitis.
4	Arthritis	More than 2 joints with pain & signs of inflammation (ie, tenderness, swelling or effusion).
4	Myositis	Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	Urinary Casts	Heme-granular or red blood cell casts.
4	Haematuria	> 5 red blood cells/high power field. Exclude stone, infection, or other causes.
4	Proteinuria	New onset or recent increase of more than 0.5 g/24 hours.
4	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	Rash	New or ongoing inflammatory lupus rash.
2	Alopecia	New or ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
2	Mucosal Ulcers	New or ongoing oral or nasal ulcerations due to active lupus.
2	Pleurisy	Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.
2	Pericarditis	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
2	Low Complement	Decrease in CH50, CC or CC below the lower limit of normal for testing laboratory.
2	Increased DNA Binding	> 25% binding by Farr assay or above normal range for testing laboratory.
1	Fever	> 38°C. Exclude infectious cause.
1	Thrombocytopenia	< 100,000 platelets/mm^3
1	Leukopenia	< 3,000 white blood cells/mm^3. Exclude drug causes.
	TOTAL SCORE	**(Sum of weights next to descriptors marked present)**

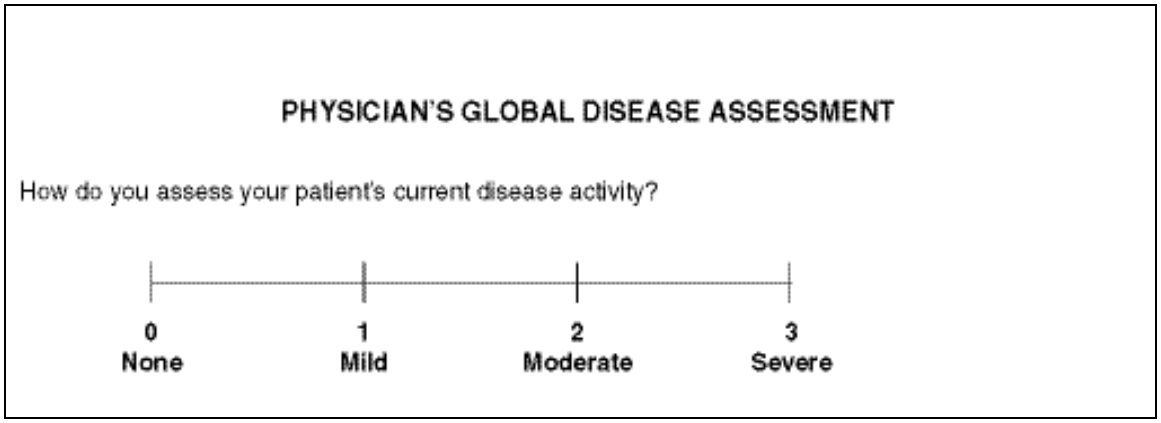
10.9. Appendix 9: SLE Flare Index

(Adapted from [Buyon, 2005; Petri, 2005; Neergaard, 2006; Petri, 1999])

Mild-moderate flare	**Severe flare**
☐ Change in SELENA SLEDAI instrument score of 3 points or more (but not to more than 12), or	☐ Change in SELENA SLEDAI instrument score to greater than 12[a], or
☐ New/worse: Discoid, photosensitive, profundus, cutaneous vasulitis, bullous lupus Nasopharyngeal ulcers Pleuritis Pericarditis Arthritis Fever (SLE) Or	☐ New/worse: CNS-SLE Vasculitis Nephritis Myositis Plt<60,000 Haemolytic anaemia with Hb<70g/L or decrease in Hb>3 g/L **Requiring**: double prednisone, or prednisone increase to >0.5mg/kg/day, or hospitalization, or
☐ Increase in prednisone, but not to >0.5 mg/kg/day, or	☐ Increase in prednisone to >0.5 mg/kg/day, or
☐ Added NSAID or hydroxychloroquine for SLE activity, or	☐ New cyclophosphamide, azathioprine, methotrexate, or mycophenolate for SLE activity, or
☐ ≥1.0 Increase in PGA score, but not to more than 2.5	☐ Hospitalisation for SLE activity, or
	☐ Increase in a PGA score to ≥2.5

a. Severe flares that are triggered only by an increase is SLEDAI Score to greater than 12 will not be categorised as severe in the analysis.

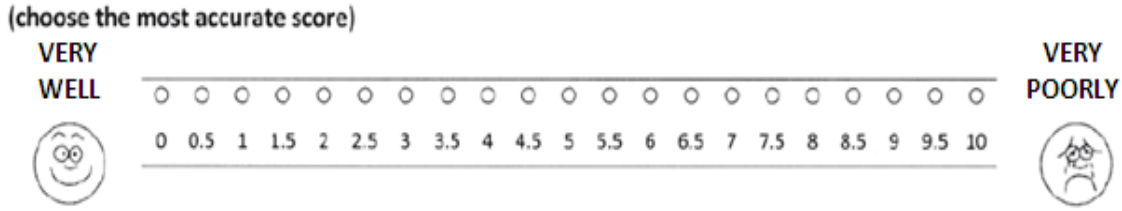
10.10. Appendix 10: Physician's Global Disease Assessment



(Adapted from [Petri, 2005])

10.11. Appendix 11: Parent's Global Disease Assessment

Considering all the ways the illness affects your child, please evaluate how he/she feels <u>at the moment</u>



10.12. Appendix 12: Protocol Amendment History

Amendment 01 （29 January 2021）

Overall Rationale for the Amendment:

This amendment specifies the criteria for primary efficacy evaluation and sample size consideration and for this criteria, adjusts the screening laboratory test for latent tuberculosis, removes the volume of blood samples for PK analysis, defines the tests conducted before informed consent would not be utilized for screening or baseline purpose, clarifies dose strength of the study intervention; specifies non-serious related AE reporting method. Additionally the following changes have been added: addition of wording to allow a repeat laboratory test for screening; requirement on recording the actual date and time of PK sample; addition of “CPK” in clinical chemistry test, clarification that PK sample will be collected when liver event happens, and addition of the missing items to the SoA according to the exclusion criteria and screening assessments.

Section # and Name	Description of Change	Brief Rationale
1.2 SOA: Safety Assessments	Addition of chest X-ray examination at screening visit.	Chest X-ray as an examination to rule out latent tuberculosis infection has not been defined in the SoA.
1.2 SOA: Laboratory Assessments	Replacement of "TSPOT" test by "QuantiFERON-TB Gold Plus" test.	The central lab only provides "QuantiFERON-TB Gold Plus" test, which has similar efficacy as "TSPOT" test in ruling out latent tuberculosis infection.
5.2 Exclusion Criteria	Replacement of "TSPOT" test by "QuantiFERON-TB Gold Plus" in exclusion criterion #25	To accommodate the availability of "QuantiFERON-TB Gold Plus" test in central lab.
5.5 Repeat Assessments during the 35 Day Screening Period	Addition of the wording to allow repeat laboratory test for screening purpose.	To reduce the probability of rescreening in cases of technical malfunction; or a value close enough to the exclusionary threshold that it may reasonably lie within the degree of variability of the assay; or if there is reason to believe the result may be false by investigator.
6.1 Study Intervention(s) Administered	Removal of the dose strength of "20 mL vial containing 400 mg lyophilised belimumab" from the table and the main content.	To clarify the dose strength used in this study.
8. Study Assessments and Procedures	Removal of the wording "Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilised for screening or Baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA".	To ensure the screening tests are conducted in same central lab and to maintain the consistency.
8.1 Screening Assessments	Addition of "chest X-ray" and "QuantiFERON-TB Gold Plus test" in screening assessments.	To keep it consistent with the requirement in exclusion criterion #25 and items in the SoA.

Section # and Name	Description of Change	Brief Rationale
8.4.1 Time Period and Frequency for Collecting AE and SAE Information	Specifies non-serious related AEs should be reported using ADR CRF to the sponsor pharmacovigilance team (qwy11935@gsk.com) via email within 5 calendar days.	Reporting form and email box has not been defined.
8.6 Pharmacokinetics	Removal of "0.5 mL" for the volume of blood samples. Addition of wording on recording the actual date and time (24-hour clock time) of each sample. Removal of the maximum amount of blood drawn for PK during this study is approximately 5 mL for each participant. Replacement of "Study Procedures Manual" with "Study Reference Manual".	The volume of blood samples will be provided in Study Reference Manual. The requirement on recording the time of PK blood sampling has not been defined. The overall volume of blood samples will be provided in Study Reference Manual. To keep consistent on the document name.
9.1 Statistical Hypotheses	Addition of the target value of the primary efficacy endpoint.	For compliance with authority's requirement.
9.2 Sample Size Determination	Addition of sample size consideration for the target value.	For compliance with authority's requirement.
10.2 Appendix 2: Clinical Laboratory Tests	Addition of "Creatine phosphokinase (CPK)" test in Clinical Chemistry of Table 3.	The CPK test required for patients with myositis has not been defined in the Appendix.
10.5 Appendix 5: Liver Safety: Required Actions and Follow-up Assessments	In Note #4, addition of quantitative Hepatitis B DNA test if positivity for HBsAg and/or HBcAb.	Quantitative Hepatitis B DNA test is required when evidences indicative of Hepatitis B infection exist.

Section # and Name	Description of Change	Brief Rationale
10.5 Appendix 5: Liver Safety: Required Actions and Follow-up Assessments	In the column of Follow Up Assessments, remove “Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) and quantitative Hepatitis B DNA”. In Note #5, removal of “PK sample may not be required for participants known to be receiving placebo or non-comparator interventions”.	This language is not applicable because patients with underlying chronic HBV will be excluded at screening. Clarification of the wording that PK sample will be collected when liver event happens.

Amendment 02 （03 June 2022）

Overall Rationale for the amendment:

One purpose of this amendment is to provide further clarity on the anti-dsDNA assay, including removal of a specific positive cut-off value as this can vary depending on the type of assay used. In addition, and to reflect current clinical practice, the requirement for a positive anti-dsDNA test, from two independent time points within the study screening period, as an Inclusion Criterion has been removed.

The other purpose is to reschedule the missing PK sampling to ensure sufficient precision of PK characterization especially during COVID pandemic period.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Delete "(≥30IU/ml)"	The anti-dsDNA positive cut-off value is dependent on the type of assay used and is established by each laboratory. See the Laboratory Specifications Document for further details.
	Delete “from 2 independent time points as follows: a) Positive test results from 2 independent time points within the study-screening period. Screening results must be based on the study’s central laboratory results. OR b) One positive historical test result and 1 positive test result during the screening period.”	To align with current clinical practice in minimizing the assessment burden on patients and to ensure consistency with the ongoing global belimumab SC paediatric study (200908).
1.2 Schedule of Activities (SoA)	Add footnote to SoA referencing for PK sampling and new wording as below, 10. If miss the sample collection on visit 3, the PK sampling should be rescheduled to any feasible visit at 7 days after dosing with ±3 days window. 11. If miss the sample collection on visit 4, the PK sampling should be rescheduled to any feasible visit at 14 days after dosing with ±7 days window. 12. If miss the sample collection on visit 7, the PK sampling should be rescheduled to when patients take the next dose.	To help investigator further understand rescheduling the missing PK sampling.

Section # and Name	Description of Change	Brief Rationale
8.6 Pharmacokinetics	Add new wording as below: If sampling for PK is missed, the impact will be minimized by attempting to reschedule the missing PK sampling to ensure sufficient precision of PK characterization in Chinese paediatric patients: • For the scenario that patients will miss the sample collection on visit 3 (Day 7±1 day), the PK sampling should be rescheduled to any feasible visit at 7 days after dosing with ±3 days window. • For the scenario that patients will miss the sample collection on visit 4 (Day 14±3 days), the PK sampling should be rescheduled to any feasible visit at 14 days after dosing with ±7 days window. • For the scenario that patients will miss the sample collection on visit 7 (Day84±7 days), the PK sampling should be rescheduled to when patients take the next dose.	To reschedule the missing PK sampling to ensure sufficient precision of PK characterization especially during COVID pandemic period.

Amendment 03 (02 January 2023)

Overall Rationale for the amendment:

The key purpose of this amendment is to add wording to clarify and reflect the connection with study 217091. Study 217091 is for participants who have completed IV treatment for 48 weeks in study 213560, and who, in the opinion of the investigator, may benefit from SC treatment with GSK1550188.

Other minor amendments are included to provide additional clarity and to reflect local GCP requirements in China.

Section # and Name	Description of Change	Brief Rationale
1.2 SOA	Update wording" N=25" to "approximately 25" in note 5, Add new wording in note 9, "If the participant transfers into study 217091, 16-week follow-up visit will not be conducted."	Add wording to ensure some operational feasibility. Add wording to reflect the connection with study 217091. To clarify that participants who transfer into study 217091 will not conduct 16-week follow-up visit.
4.1. Overall Design	Add new wording as below, "Participants completed the last Benlysta IV administration at Week 48 and transfer to study 217091 successfully will continue to complete the 52-week visit of 213560. However, 16-week follow-up visit will not be conducted."	To reflect the connection with study 217091 and clarify that participants who transfer into study 217091 will not conduct 16-week follow-up visit of study 213560.
4.2.Scientific Rationale for Study Design	Update wording in the 5th paragraph, "target N=25" update to "approximately 25"	Add wording to ensure some operational feasibility.
4.4. End of Study Definition	Add new wording as below: "For participants switch to study 217091, the end of the study defined as completed Week 52 visit."	Add wording to reflect the connection with study 217091. To clarify that participants who transfer into study 217091 will not conduct 16-week follow-up visit and the end of study 213560 defined as completed Week 52 visit.
6.5.2. Prohibited Medications and Non-Drug Therapies	Add new wording, "except study 217091"	Allow participants to transfer to study 217091.
6.7. Intervention after the End of the Study	Add new wording as below, "Participants completed the last Benlysta IV administration at Week 48 and transfer to study 217091 successfully will continue to complete the 52-week visit of 213560. However, 16-week follow-up visit will not be conducted."	Add wording to reflect the connection with study 217091. To clarify that participants who transfer into study 217091 will not conduct 16-week follow-up visit of study 213560.

7.1 Discontinuation of Study Intervention	Add new wording “except study 217091.”	Allow participants to transfer to study 217091.
10.2. Appendix 2: Clinical Laboratory Tests	Delete wording, “or by the local laboratory” “In the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation, local laboratory results could be considered. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.“	Double sampling does not comply with local EC policy. The study operation execution will follow local clinical practice. Delete the wording to avoid misunderstanding.

11. REFERENCES

Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI: a disease activity index for lupus subjects. The Committee on Prognosis Studies in SLE. Arthritis Rheum. 1992;35(6):630-40.

Buyon JP, Petri MA, Kim MY, et al. The Effect of Combined Estrogen and Progesterone Hormone Replacement Therapy on Disease Activity in Systemic Lupus Erythematosus: A Randomised Trial. Ann Internal Med. 2005;142(12 Pt 1):953-62.

Cheema DS, Roschke V, Hilbert DM, et al. Elevated serum B-lymphocyte stimulator levels in subjects with systemic immune-based rheumatic diseases. Arthritis Rheum. 2001;44(6):1313-9.

Eibl MM, Rosen FS. Intravenous gamma globulin and plasmapheresis. In: Frank MM (ed). Samter's Immunologic Diseases (5th ed.). Boston:Little, Brown, 1995:1529-36.

Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63(12):3918-30.

Goldfarb NS, Avery RK, Goormastic M, et al. Hypogammaglobulinemia in lung transplant recipients. Transplantation. 2001;71(2):242-6.

GSK document number 2011N128591_06 - Belimumab Investigator's Brochure. 22-MAY-2020

GSK document number 2017N34326_00 - 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) – Double-Blind Endpoint Analysis (Part A).09-JUL-2018.

GSK document number 2020N427517_00 - Prediction of Intravenous GSK1550188 (Belimumab) Dose-Exposure Relationship in Chinese Paediatric Patients with Systemic Lupus Erythematosus. 27-DEC-2019.

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.

Hong SD, Reiff A, Yang H, et al. B Lymphocyte Stimulator Expression in Pediatric Systemic Lupus Erythematosus and Juvenile Idiopathic Arthritis Subjects, Arthritis & Rheum. 2009; 60(11): 3400–3409

Liang M, Fortin P, Schneider M, et al. Ad Hoc Working Group on Steroid-Sparing Criteria in Lupus. Criteria for Steroid-Sparing Ability of Interventions in Systemic Lupus Erythematosus. Arthritis and Rheumatism 2004;50,pp 3427–3431

Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9767):721-31.

Neergaard. Reducing the risk of blood thinners. Associated press, September 2006.

Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus. 1999;8:685-91.

Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med. 2005;353:2550-8.

Petri M, Stohl W. Chatham W, et al. Association of plasma B-Lymphocyte stimulator (BLyS) levels and disease activity in systemic lupus erythematosus. Arthritis Rheum 2008; 58(8):2453-9.

Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009 Mar;20(3):629-37.

Stichweh D, Arce E, Pascual V. Update on pediatric systemic lupus erythematosus. Curr Opin Rheumatol. 2004 Sep;16(5):577-87.

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

Stohl W, Schwarting A, Okada M, et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two-week randomized, double-blind, placebo-controlled study. Arthritis Rheumatol. 2017;69(5):1016-27.

Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25(11):1271-7.

Thakral A, Klein-Gitelman MS. An Update on Treatment and Management of Pediatric Systemic Lupus Erythematosus. Rheumatol Ther. 2016 Dec;3(2):209-219.

U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010).

Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 2008;84(5):548-58.

Wang Y, Jadhav PR, Lala M, et al. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. Jr Clin Pharmacol. 2012;52(10):1601-6.

Yamani MH, Avery RK, Mawhorter SD, et al. Hypogammaglobulinemia following cardiac transplantation: a link between rejection and infection. J Heart Lung Transplant. 2001;20(4):425-30.

BENLYSTA™ (belimumab) injection, for intravenous use. Package Insert. 02 December 2020 (Chinese).

Signature Page for 213560 TMF-17745556 v1.0

Reason for signing: Approved	Name: PPD Role: A Date of signature: 22-Jan-2024 17:13:10 GMT+0000

Signature Page for TMF-17745556 v1.0