TITLE PAGE

Protocol Title:

A Multi-Centre, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subcutaneously Administered Belimumab Plus Standard Therapy in Chinese Paediatric Participants with Systemic Lupus Erythematosus (SLE)

Protocol Number: 217091 / Amendment 02

Compound Number or Name: GSK1550188

Brief Title: Evaluate Pharmacokinetics of Subcutaneous Belimumab in Chinese Paediatric Participants with Systemic Lupus Erythematosus (SLE).

Study Phase: Phase 1

Sponsor Name and Legal Registered Address:

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

Manufacturer:

The autoinjector components are manufactured by Scandinavian Health Limited (SHL) and assembled with the pre-filled syringe at GlaxoSmithKline (GSK), Barnard Castle, United Kingdom (UK).

Regulatory Agency Identifying Number(s):NA

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

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

Approval Date: 24 Jan 2024

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 02	24 Jan 2024
Amendment 01	3 Jan 2023
Original protocol	31 Jan 2022

Amendment 02:24 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 current 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	Move the section from 10.8 of previous version (amend 01) to the beginning of the protocol Delete Trademark Information Addition or update of definitions for several terms, including Investigational Product, Standard of Care, Background treatment, Adverse Drug , Reaction, SUSAR, Legal guardian	To comply with an update to the internal GSK protocol process and template.
10.6 Appendix 6: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart/Rechallenge Guidelines	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.
10.8. Appendix 8: Protocol Amendment History	Add a section to overview protocol amendment history	Overview protocol amendment history.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibodies
ADE	Adverse device effect
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUCss, 0-τ	Area under the curve at steady-state to the end of the dosing period
BLyS	B lymphocyte Stimulator
BW	Body weight
Cavg	Average concentration
Cavgss	Average serum concentration at steady state
CDE	Centre for Drug Evaluation
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
Cmax	Maximum concentration
Cmaxss	Maximum serum concentrations during the dosing interval at steady state
Cmin	Minimum concentration
Cminss	Minimum serum concentrations at steady state
CPK	Creatinine phosphokinase
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
dL	Deciliter
eCRF	Electronic case report form
ECG	Electrocardiogram
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Glutamyl transferase
GSK	GlaxoSmithKline
HB	Hepatitis B
HBsAg	Hepatitis B surface antigen
HBc	Hepatitis B core

HBcAb	Hepatitis B core antibody
HGS	Human Genome Sciences, Inc
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
Hpf	High power field
HRT	Hormonal replacement therapy
IA	Intraarticular
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL-6	Interleukin-6
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIV	Inter-individual variability
IM	Intramuscular
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWRS	Interactive web response system
Kg	Kilogram
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
Mg	Milligram
mL	Milliliter
MCID	Minimally clinically important difference
□g	Microgram
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDR	Medical Device Regulation
MMF	Mycophenolate mofetil
MSDS	Materials Safety Data Sheet
N/A	Not applicable
NDA	New drug application
NSAIDs	Non-steroidal anti-inflammatory drugs
PAC	Post approval commitment
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PML	Progressive multifocal encephalopathy
PO	By mouth (per os)

PT	Prothrombin time
PTT	Partial thromboplastin time
QTL	Quality tolerance limits
QW	Once a week
Q10D	Every 10 days
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RA	Rheumatoid arthritis
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
SADE	Serious adverse device effect
SAE	Serious Adverse Event
SC	Subcutaneous/subcutaneously
SELENA	Safety of Estrogen in Lupus Erythematosus National Assessment
SFI	SLE Flare Index
SHL	Scandinavian Health Limited
cSLE	Childhood Onset Systemic Lupus Erythematosus
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SoA	Schedule of Activities
SOC	System Organ Classes
SRI	SLE Responder Index
SRM	Study Reference Manual
TNF	Tumor Necrosis Factor
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USA	United States of America
USADE	Unanticipated SADE
WBC	White blood cell
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.

legal guardian	Parent(s) (preferably both if available or as per local requirements), legally appointed guardian(s), or legally acceptable representative(s), as defined by national and local laws and regulations, who consent(s) on behalf of the minor. For the purposes of this study, all references to informed consent and assent refer to the pediatric participant (child) and his or her legal guardian who have provided consent (and assent as applicable) according to the Informed Consent Process and Assent Form described in Section 10.1.3 Informed Consent and Assent Process

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Multi-Centre, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subcutaneously Administered Belimumab Plus Standard Therapy in Chinese Paediatric Participants with Systemic Lupus Erythematosus (SLE)

Brief Title: Evaluate Pharmacokinetics of Subcutaneous Belimumab in Chinese Paediatric Participants with Systemic Lupus Erythematosus (SLE).

Rationale: The purpose of this study is to evaluate the pharmacokinetic (PK) characteristics and safety of repeat doses of 200 mg belimumab subcutaneous (SC) in Chinese paediatric participants by leveraging the China belimumab IV paediatric study (213560), such that paediatric participants completing 48 weeks belimumab IV treatment could be rolled over to this belimumab SC study. The PK data derived from this study will contribute to the update of previous population PK model, and on the basis of the updated population PK model, an appropriate dose regimen of belimumab SC (i.e., dose frequency according to body weight) for Chinese paediatric participants will be determined by simulation.

Objectives and Endpoints and Estimands:

Objectives	Endpoints
Primary - Pharmacokinetics	
• To characterize belimumab exposure following belimumab 200 mg SC in Chinese paediatric systemic lupus erythematosus (SLE) participants who have previously been treated with IV belimumab	• Exposure parameters: $AUC_{ss, 0-\tau}$, $C_{avg, ss}$, $C_{min, ss}$, $C_{max, ss}$
Secondary - Safety	
• To evaluate the safety and tolerability of belimumab 200mg SC in paediatric participants with SLE who have previously been treated with IV belimumab	• Occurrence of adverse events, serious adverse events and adverse events of special interest through Week 12.

AUCss, 0-τ = Area under the curve at steady-state to the end of the dosing period, Cavg, ss= Average serum concentration at steady state, Cmin, ss = Minimum serum concentrations at steady state, Cmax, ss = Maximum serum concentrations during the dosing interval at steady state

Overall Design:

This is a single arm, multi-centre open label study of belimumab plus standard of care in participants with SLE who have completed 48 weeks belimumab IV treatment in 213560

study, to evaluate the PK and safety of subcutaneously administered belimumab over 12 weeks in approximately 17 paediatric participants aged 5-17 years and weighing ≥15 kg.

Brief Summary:

213560 study is an open label study to evaluate the safety, efficacy and pharmacokinetics of belimumab (10 mg/kg) IV with standard therapy in Chinese paediatric participants aged 5 to 17 years with active SLE. The participants in study 217091 will be those who have completed the 48-week treatment of 213560 study and who, in the investigator's judgement will benefit from continuing treatment with belimumab. The targeted aim for this study will be to recruit participants in study 213560 who have IV PK samples collected. However, if the targeted number of participants cannot be met, additional participants from the non-PK population in 213560 will also be included. The PK sample right after the last IV dose in 213560 and pre-dose PK sample of study 217091 will be collected from each patient to ensure the belimumab PK profile leading up to and following the switch to SC dosing can be accurately characterized for each participant.

Participants who have completed Week 52 assessment in study 213560, will receive the first SC dose in study 217091 no more than 4 weeks after the last IV dose (administered at week 48 visit of study 213560). The study will include:

- Open-label, 12-week treatment phase.
- Post-treatment follow-up assessments at 8 weeks and 16 weeks after the last dose of SC belimumab

Number of Participants:

Approximately 17 participants will be enrolled to study intervention.

Note: Enrolled means a participant's (if applicable) and their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Intervention Groups and Duration:

The total maximum duration of study participation for each participant is 33 weeks (screening:5 weeks, treatment: up to 12 weeks and follow-up: 16 weeks).

Administration of belimumab 200 mg SC will be as follows:

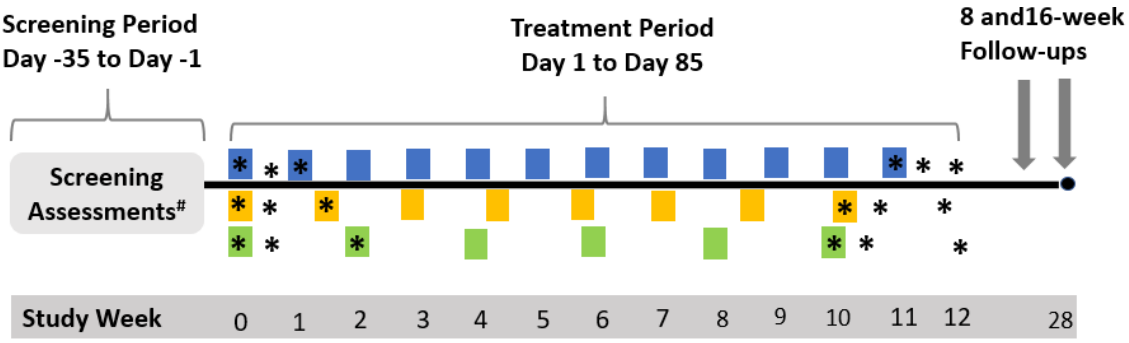
- Participants ≥50 kg body weight will receive belimumab 200 mg SC weekly.
- Participants ≥30 kg to <50 kg body weight will receive belimumab 200 mg SC every 10 days.

- Participants ≥15 kg to <30 kg body weight will receive belimumab 200 mg SC every 2 weeks.

The dosing frequency fixed according the baseline body weight.

Data Monitoring/ Other Committee: No

1.2. Schema



Participants ≥50 kg body weight will receive belimumab 200 mg SC weekly
Participants ≥30 kg to <50 kg body weight will receive belimumab 200 mg SC every 10 days
Participants ≥15 kg body to <30 kg weight will receive belimumab 200 mg SC every 2 weeks

* PK sampling
# Participants will roll over from study 213560 thus the screening period of this study will have an overlap with study 213560.

Note: For those participants who don't have PK samples in study 213560, 3 additional PK samples will be collected within 4 hours, at 7 days (±2 days) and 14 days (±2 days) after last belimumab IV infusion at Week 48 of study 213560.

1.3. Schedule of Activities (SoA)

1.3.1. Body weight ≥50 kg, Dose 200 mg QW

Body weight ≥50 kg, Dose 200 mg QW														
Site Visit	**V1**	**V2**	**V3**	**V4**	**V5, V6**	**V7**	**V8-10**	**V11**	**V12-13**	**V14**	**V15**	**V16**	**V17**	**V18**
Procedure	**Screening**	**Treatment Period (12 weeks)**											**Follow-Up Period[1,2]**	
Study Day/Week	**-35 days**	**Day 1**	**Day 4±1**	**Day 8±2**	**Day 15, 22 ±2**	**Day 29±2**	**Day 36, 43, 50±2**	**Day 57±2**	**Day 64, 71±2**	**Day 78±1**	**Day 81±1**	**Day 85±2 / EW[1]**	**8-Week± 7 -Day Follow up[1]**	**16-Week ±7-Day Follow -up[1,2]**
		Wk 0		**Wk 1**	**Wk 2-3**	**Wk 4**	**Wk 5-7**	**Wk 8**	**Wk 9-10**	**Wk 11**		**Wk 12**		
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	
Symptom Driven Physical Exam[3]	X	X				X		X				X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X[6]		X	X	X	X	X	X	X		X	X	
Height		X				X		X				X	X	
12-Lead ECG	X													

Body weight ≥50 kg, Dose 200 mg QW														
Site Visit	**V1**	**V2**	**V3**	**V4**	**V5, V6**	**V7**	**V8-10**	**V11**	**V12-13**	**V14**	**V15**	**V16**	**V17**	**V18**
Procedure	**Screening**	**Treatment Period (12 weeks)**											**Follow-Up Period[1,2]**	
Study Day/Week	**-35 days**	**Day 1**	**Day 4±1**	**Day 8±2**	**Day 15, 22 ±2**	**Day 29±2**	**Day 36, 43, 50±2**	**Day 57±2**	**Day 64, 71±2**	**Day 78±1**	**Day 81±1**	**Day 85±2 / EW[1]**	**8-Week± 7 -Day Follow up[1]**	**16-Week ±7-Day Follow -up[1,2]**
		Wk 0		**Wk 1**	**Wk 2-3**	**Wk 4**	**Wk 5-7**	**Wk 8**	**Wk 9-10**	**Wk 11**		**Wk 12**		
Adverse Events		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
Device Incidents malfunctions		X		X	X	X	X	X	X	X		X		
Laboratory Assessments														
Haematology	X[5]	X[5]				X		X				X	X	
Chemistry	X[5]	X[5]				X		X				X	X	
Urinalysis	X[5]	X[5]				X		X				X	X	
Pregnancy Test[4]	X[5]	X[5]				X		X				X	X	
IgA, IgG and IgM	X	X[5]				X		X				X	X	
Belimumab Administration and PK Sampling														
PK Sampling	X[7]	X[8]	X[10]	X[8, 11]						X[8]	X	X		
Administration of Belimumab		X[9]		X[9]	X	X	X	X	X	X				

1.3.2. Body weight ≥30 kg - <50 kg, Dose 200 mg Q10d

Site Visit	V1	V2	V3	V4	V5	V6	V7, V8	V9	V10	V11	V12	V13	V14
Procedure	**Screening**	**Treatment Period (12 weeks)**										**Follow-Up Period[1,2]**	
Study Day/Week	**-35 days**	**Day 1**	**Day 4± 1**	**Day 11± 2**	**Day 21± 2**	**Day 31± 2**	**Day 41, 51± 2**	**Day 61± 2**	**Day 71± 1**	**Day 74± 1**	**Day 81± 2 / EW[1]**	**8-Week ±7-Day Follow-up[1]**	**16-Week± 7-Day Follow-up**
Informed consent	X												
Inclusion and exclusion criteria	X												
Demography	X												
Medical history	X												
Concomitant Medication	X	X		X	X	X	X	X	X		X	X	
Symptom Driven Physical Exam[3]	X	X				X		X			X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X[6]		X	X	X	X	X	X		X	X	
Height		X						X			X	X	
12-Lead ECG	X												
Adverse Events		X		X	X	X	X	X	X		X	X	X
Serious Adverse Events		X		X	X	X	X	X	X		X	X	X
Device Incidents malfunctions		X		X	X	X	X	X	X		X		
Haematology	X[5]	X[5]				X		X			X	X	
Chemistry	X[5]	X[5]				X		X			X	X	
Urinalysis	X[5]	X[5]				X		X			X	X	

Site Visit	V1	V2	V3	V4	V5	V6	V7, V8	V9	V10	V11	V12	V13	V14
Procedure	**Screening**	**Treatment Period (12 weeks)**										**Follow-Up Period[1,2]**	
Study Day/Week	**-35 days**	**Day 1**	**Day 4± 1**	**Day 11± 2**	**Day 21± 2**	**Day 31± 2**	**Day 41, 51± 2**	**Day 61± 2**	**Day 71± 1**	**Day 74± 1**	**Day 81± 2 / EW[1]**	**8-Week ±7-Day Follow-up[1]**	**16-Week± 7-Day Follow-up**
Pregnancy Test[4]	X[5]	X[5]				X		X			X	X	
IgA, IgG and IgM	X	X[5]				X		X			X	X	
PK Sampling	X[7]	X[8]	X[10]	X[8, 11]					X[8]	X	X		
Belimumab administration		X[9]		X[9]	X	X	X	X	X				

1.3.3. Body weight ≥15 kg - <30kg, Dose 200 mg Q2W

Site Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Procedure	**Screening**	**Treatment Period (12 weeks)**									**Follow-Up Period[1,2]**	
Study Day/Week	**-35 days**	**Day 1**	**Day 4±1**	**Day 15±2**	**Day 29±2**	**Day 43±2**	**Day 57±2**	**Day 71±1**	**Day 74±1**	**Day 85±2 /EW[1]**	**8-Week ±7-Day Follow-up[1]**	**16-Week±7-Day Follow-up[1,2]**
		Wk 0		**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**		**Wk 12**		
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	

Site Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Procedure	**Screening**	**Treatment Period (12 weeks)**									**Follow-Up Period[1,2]**	
Study Day/Week	**-35 days**	**Day 1**	**Day 4±1**	**Day 15±2**	**Day 29±2**	**Day 43±2**	**Day 57±2**	**Day 71±1**	**Day 74±1**	**Day 85±2 /EW[1]**	**8-Week ±7-Day Follow-up[1]**	**16-Week±7-Day Follow-up[1,2]**
		Wk 0		**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**		**Wk 12**		
Symptom Driven Physical Exam[3]	X	X			X		X			X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X[6]		X	X	X	X	X		X	X	
Height		X			X		X			X	X	
12-Lead ECG	X											
Adverse Events		X		X	X	X	X	X		X	X	X
Serious Adverse Events		X		X	X	X	X	X		X	X	X
Device Incidents malfunctions		X		X	X	X	X	X		X		
Laboratory Assessments												
Haematology	X[5]	X[5]			X		X			X	X	
Chemistry	X[5]	X[5]			X		X			X	X	
Urinalysis	X[5]	X[5]			X		X			X	X	
Pregnancy Test[4]	X[5]	X[5]			X		X			X	X	
IgA, IgG and IgM	X	X[5]			X		X			X	X	
Belimumab Administration and PK Sampling												
PK Sampling	X[7]	X[8]	X[10]	X[8, 11]				X[8]	X	X		
Administration of Belimumab		X[9]		X[9]	X	X	X	X				

ECG: Electrocardiogram, IgA: Immunoglobulin A, IgG: Immunoglobulin G, IgM: Immunoglobulin M, PK: Pharmacokinetic. Note:

1. 8-week and 16-week follow-up is required for participants who withdraw from study treatment prior to Week 12 (Month 3) or completed 12 weeks of treatment. For participants who withdraw from treatment prior to Week 12 (Month 3), in addition to the 8-week and 16-week follow-up visit and assessments, an early withdrawal visit (EW) should be completed within 4 weeks of the decision to withdraw. The EW visit requires identical assessments and procedures to the Week 12 visit (Month 3).
2. The 16-week follow-up requires a phone call to collect adverse events (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.
3. Full Physical Examination is required at screening. An abbreviated/symptom-driven exam can be done thereafter as described in Section 8.3.1.
4. Serum pregnancy test required at screening for all females of childbearing potential. Urine pregnancy test is sufficient for all subsequent visits. A home pregnancy test (urine) will be provided to participants for the 16-week follow-up pregnancy assessment.
5. Laboratory assessments in visit 1 (screening) and visit 2 (Day 1) would share with study 213560 visit 16 (Week 48) and visit 17 (Week 52) laboratory assessments respectively.
6. The participant's weight at Day 1 should be calculated to decide dosing frequency for each following visit to be administered.
7. For those participants who don't have IV PK samples in study 213560, 3 additional PK samples will be collected within 4 hours, at 7 days (±2 days) and 14 days (±2 days) after last belimumab IV infusion at week 48 of study 213560.
8. Samples must be taken pre-dose.
9. For the first 2 doses participants must be observed for 3 h post belimumab injection.10. If the PK sample collection on visit 3 was missed, then that PK sample collection should be rescheduled at 3 ±1 day after any of the next doses.
11. If the PK sample collection on visit 4 was missed, then that PK sample collection should be rescheduled to when participants take the next dose and the sample must be taken pre-dose.

2. INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with multisystem involvement characterised by autoantibody production and abnormal B lymphocyte function. Paediatric SLE shares similar pathogenesis with adult SLE that includes a complex interaction of genetics, environment, and hormones that leads to immune-tolerance damage, resulting in autoantibody production, inflammation and organ injury.

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 IV was first approved in the United States of America (USA) in 2011 as an add-on treatment for adult participants with active autoantibody positive SLE despite standard therapy. It is now approved in over 70 countries. Belimumab IV 10mg/kg for the treatment of SLE in paediatric population from 5-17 years of age was approved in the United States (US), Japan and the European Union (EU) in 2019 and in China on 02 December 2020.

Belimumab 200 mg once weekly SC administered injection formulation (ready to use pre-filled syringe and autoinjector) was first approved in July 2017 in the US and is now licensed in over 30 countries. The New drug application (NDA) of Belimumab SC for adult SLE in China was accepted by China's Centre for Drug Evaluation (CDE) on 01 December 2020. An oversea bridging PK study (200908) is currently ongoing to evaluate the pharmacokinetics (PK), safety, and pharmacodynamics (PD) of 200 mg belimumab SC in paediatric participants 5 to 17 years of age with SLE. Data generated from the current study (217091) using the SC formulation in Chinese paediatric participants ages 5-17 years will be estimated via a population PK approach to determine a dosing regimen for Benlysta 200 mg solution for SC injection that enables appropriate exposures to be reached to achieve efficacy in Chinese children with SLE.

2.1. Study Rationale

The purpose of this study is to evaluate the pharmacokinetic characteristics and safety of repeat doses of 200 mg belimumab subcutaneous in Chinese paediatric participants by leveraging the China belimumab IV paediatric study (213560), such that paediatric participants completing 48 weeks belimumab IV treatment can switch to SC treatment by joining the SC PK bridging study. The PK data derived from this study will contribute to the update of previous population PK model, and on basis of the updated population PK model, appropriate dose regimen of belimumab SC (i.e., dose frequency according to body weight) for Chinese paediatric participants will be determined by simulation.

2.2. Background

Paediatric SLE is an important subgroup of lupus, manifested as an autoimmune disease with multisystem involvement characterized by widespread inflammation of blood vessels and connective tissue [Petty, 2005]. Paediatric SLE is often treated with high doses of corticosteroids and immunosuppressant's including IV cyclophosphamide than adult SLE, contributing to the increased incidence and earlier onset of long-term organ damage in children [Mina, 2013, Chatham , 2001; Silva, 2016]. Development of safe and

effective treatments for paediatric SLE therefore remains an area of high-unmet need. Belimumab was first approved for adults in 2011 in the USA, which can not only reduce disease activity and SLE flares but also reduce the dosage of steroids [Furie, 2011; Navarra, 2011; Stohl, 2012]. Although the IV formulation of belimumab is approved for the treatment of adult and paediatric participants in China, the SC formulation is still particularly needed to allow at-home administration and reduce the burden of IV infusion and consequently required hospital visits for participants, their families and hospitals.

Further information on the safety and efficacy of belimumab is provided in the current IB and investigator's brochure (IB) supplement(s) (if applicable) and product label.

2.2.1. Efficacy of IV Belimumab in Paediatric SLE participants

Belimumab efficacy in SLE participants has been established in Chinese adults with SLE in the adult IV study in Northeast Asia (BEL113750) and has been demonstrated to be comparable to efficacy in overseas adults (C1056, C1057, BEL112341) and overseas paediatrics (BEL114055). Therefore, a comparable efficacy would be expected in paediatric participants from China.

The SLE Responder Index (SRI) Response rate at Week 52 in study BEL114055 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 participants 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 participants (95% CI: 0.42, 4.18) to OR 1.67 in Asian participants (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.

2.2.2. Safety of IV Belimumab in Paediatric SLE participants

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 studies) and the North East Asian adult studies (BEL113750). Also, consistency was demonstrated between paediatric and adult studies safety results.

The safety of belimumab in paediatric participants has been evaluated in the double-blind phase of study BEL114055, 82.5% of participants experienced at least 1 AE in placebo group and 79.2% in the belimumab 10 mg/kg group. 35.0% of participants experienced at least 1 serious adverse events (SAE) in placebo group and 17.0% in the belimumab group. The system organ class (SOC) with the highest incidence of SAEs was infections and infestations (12.5%, placebo; 7.5%, belimumab). Adverse events of special interest (AESI) 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 participants in either treatment group experienced an AESI of malignancy. 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%) participant in the placebo group experienced a fatal SAE (pancreatitis acute), while no death occurred in the belimumab group.

2.2.3. Pharmacokinetics of IV 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, 200909 and 209629). Population PK analyses have been conducted in both adults (Report No. HGS1006-POPPK) and paediatrics (BEL114055 POPPK). The results showed belimumab PK to be body-weight-dependent, dose-proportional and time-invariant after IV administration, similar to many monoclonal antibodies targeting soluble ligands. Geometric mean values of steady-state maximum concentration (Cmax), minimum concentration (Cmin), average concentration (Cavg), and area under the curve (AUC) were estimated to be 315 µg/mL, 50 µg/mL, 108 µg/mL, and 3012 day • µg/mL respectively 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, indicating no great difference exists in steady-state exposure between paediatric and adult populations. The slightly decreased exposure in younger participants was expected due to the allometric effect of lower body weight combined with weight proportional dosing. Because of body weight difference between Asian and Caucasian adult participants, there is small difference in exposure of belimumab when the same weight proportional 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].

2.2.5. Belimumab IV in Chinese paediatric SLE Participants (Study 213560)

The registration of Benlysta for paediatrics in China, approved in December 2020, was based on extrapolation of efficacy from results of the overseas paediatric population study (BEL114055), the Northeast Asian Phase 3 study with Chinese adult data (BEL113750) and other overseas Phase 3 studies (C1056, C1057). Following a requirement from CDE, GSK is conducting a post approval commitment (PAC) study (213560) to further evaluate the effectiveness, safety and PK profile of belimumab IV in Chinese paediatric SLE participants. Study 213560 is a multi-centre, open-label study targeting to enrol approximately 65 Chinese paediatric participants with active SLE aged 5 to 17 years, and to characterise the pharmacokinetic profile in a subset (target N=25) of

the study population. 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.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of belimumab may be found in the current IB 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 encephalopathy (PML). Fatal infections have been reported in participants with SLE 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, IgA deficiency (IgA level <10 mg/dL), acute or chronic infections requiring management, serologic evidence of Hepatitis B, Hepatitis C or Human immunodeficiency virus (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 10.2 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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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.
SC Injection-Related reactions, Hypersensitivity Reactions and Immunogenicity		
Administration of belimumab may result in infusion or injection-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 no relationship to anti-drug antibody (ADA) has been established. Infusion or injection-related systemic reactions and hypersensitivity reactions occur more frequently with the first two doses and tend to decrease with subsequent doses. In studies involving subcutaneous administration, injection site reactions occurred more frequently following subcutaneous administration than with intravenous infusion. The most frequent	Participants with a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins, or monoclonal antibodies or to any of the excipients of the study drug will be excluded from this study. Participants will remain under clinical supervision for 3 hours after completion of the first 2 belimumab injections. Participants will be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Participants will be given an alert card for hypersensitivity/allergic reactions.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	injection site-related event was pain at the site of injection.	
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 participants for signs and symptoms of malignancy, monitor laboratory values, request that participants report signs and symptoms. Treat appropriately.
Interactions with Vaccinations		
Because of its mechanism of action, belimumab may interfere with the response to immunizations.	The efficacy of concurrent vaccination in participants 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 Participants with SLE receiving belimumab compared with those not receiving treatment at the time of vaccination.	Immunization with live or live attenuated vaccines is prohibited from 30 days prior to Day 1 and during belimumab use. Participants' vaccination status should be assessed and current immunization guidelines followed; all necessary vaccinations should be administered no later than 30 days prior to Day 1.
Psychiatric Events		
Psychiatric events including depression and suicidality.	In a recent one-year, randomized, double-blind, placebo-controlled post marketing study (BEL115467) of 4,003 participants with SLE (1:1 randomization): Serious adverse events (SAE) of suicidal ideation or behavior or self-injury	Participants who, in the investigator's opinion, pose a significant suicide risk will be excluded. Monitor participants for psychiatric signs and symptoms, request that participants report

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	were reported in 0.7% (n= 15) of participants receiving belimumab intravenously 10 mg/kg (IV) vs. 0.2% (n=5) of participants taking placebo. No suicide-related deaths were reported. SAEs of depression were reported in 0.3% (n=7) of participants 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) participants on belimumab 10 mg/kg IV reported suicidal ideation or behavior and 2.0% (n=39) participants on placebo reported suicidal ideation or behavior.	psychiatric symptoms. Treat psychiatric symptoms immediately and appropriately.
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.
Autoinjector device		
Injury due to injection device, i.e., needle stick injury, intradermal injection, intramuscular injection, and/or infection at injection site due to improper cleaning of site and/or contamination of injection needle during handling (e.g., dropped onto floor).	A comprehensive risk assessment for use of the devices during self-administration has been performed in accordance with International Organization for Standardization (ISO) 14971, “Application of Risk Management to Medical Devices.” Accordingly, all potential risks posed by the user during operation of device for self-administration have been identified and evaluated.	The participant and their caregiver will be educated by the staff prior to self-administration and their first 3 scheduled doses will be supervised in the clinic.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	The possible risks identified are based on those observed during formative human factors studies, benchmarking similar devices on the market, and theoretical misuse scenarios. For those risks identified as unacceptable, risk control measures have been identified and implemented to mitigate the risk through optimizing the device design and/or instructions for use.	

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 participants with SLE (BEL114055) was consistent with that seen in adult participants.

2.3.3. Overall Benefit: Risk Conclusion

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

3. OBJECTIVES AND ENDPOINTS AND/OR ESTIMANDS

Objectives	Endpoints
Primary - Pharmacokinetics	
• To characterize belimumab exposure following belimumab 200 mg SC in Chinese paediatric systemic lupus erythematosus (SLE) participants who have previously been treated with IV belimumab	• Exposure parameters; $AUC_{ss,\ 0\text{-}\tau}$, $C_{avg,ss}$, $C_{min,ss}$, $C_{max,ss}$,
Secondary - Safety	
• To evaluate the safety and tolerability of belimumab 200mg SC in paediatric Participants with SLE who have previously been treated with IV belimumab	• Occurrence of adverse events, serious adverse events and adverse events of special interest through Week 12.

AUCss, 0-τ = Area under the curve at steady-state to the end of the dosing period, Cavg, ss= Average serum concentration at steady state, Cmin, ss = Minimum serum concentrations at steady state, Cmax, ss = Maximum serum concentrations during the dosing interval at steady state

Primary estimands

For estimand strategy in primary endpoint. The estimand is described by the following attributes:

Population	Chinese paediatric participants 5-17 years of age with SLE who have previously been treated with IV belimumab
Treatment	• Repeat doses of 200mg belimumab administered SC over 12 weeks on a background of standard of care therapy
Endpoints	• Exposure parameters; $AUC_{ss,\ 0\text{-}\tau}$, $C_{avg,ss}$, $C_{min,ss}$, $C_{max,ss}$,
Summary Measure	• Geometric mean
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies are: • Discontinuation of study medication: while-on-treatment strategy. The PK data after study medication discontinuation (except for PK data from EW visit) will not be used in analysis. Specially, to maximize PK data to support the estimation of

	exposure parameters, the PK data from EW visit will be used in analysis. • Interruption of study medication: treatment policy strategy. The PK data after interruption of study medication will be used in analysis. • Using of prohibited medications or therapies: while-on-treatment strategy. Only the PK data before initiation of prohibited medications or therapies will be used in analysis.

Rationale for estimand: Interest lies in the exposure parameters when participants have actually taken study medication irrespective of interruption of study medication. For using of prohibited medications or therapies, the while-on-treatment strategy is motivated by the potential confounding of PK data after using prohibited medications or therapies.

For estimand strategy in secondary endpoint. The estimand is described by the following attributes:

Population	Chinese paediatric participants 5-17 years of age with systemic lupus erythematosus (SLE) who have previously been treated with IV belimumab
Treatment	• Repeat doses of 200mg belimumab administered subcutaneously (SC) over 12 weeks on a background of standard of care therapy
Endpoints	• Occurrence of adverse events, serious adverse events and adverse events of special interest through Week 12.
Summary Measure	• Frequency and percentage
Intercurrent events and strategies	• Discontinuation of study medication, addressed with while-on-treatment strategy. Safety data in the 12-week on-treatment period will be used in analysis. The definition of on-treatment period will be provided in reporting and analysis plan (RAP).

Rationale for Estimand: This attempts to estimate on-treatment safety effects likely to be attributable to the drug.

In addition to estimand strategy in secondary endpoint, an additional analysis will be performed based on all safety data including 12-week on-treatment period and 16-week post-treatment follow-up period.

Further details on estimand strategy will be provided in the RAP.

4. STUDY DESIGN

4.1. Overall Design

This is a single arm, multi-centre open label study of belimumab plus standard of care in participants with SLE who have completed 48 weeks belimumab IV treatment in 213560 study to evaluate the PK and safety of subcutaneously administered belimumab over 12 weeks in approximately 17 paediatric participants ages 5-17 years and weighing ≥15 kg.

213560 study is an open label study to evaluate the safety, efficacy and pharmacokinetics of belimumab (10 mg/kg) IV with standard therapy in Chinese paediatric participants aged 5 to 17 years with active SLE. The participants in study 217091 will be those who have completed the 48-week treatment phase of 213560 study and who, in the investigator's judgement will benefit from continuing treatment with belimumab. The targeted aim for this study will be to recruit participants in Study 213560 who have IV PK samples collected. However, if the targeted number of participants cannot be met additional participants from the non-PK population in 213560 will also be included. The PK sample right after the last IV dose in 213560 and pre-dose PK sample of study 217091 will be collected from each patient to ensure the belimumab PK profile leading up to and following the switch to SC dosing can be accurately characterized for each participant.

Participants who have completed Week 52 assessment in study 213560, will receive the first SC dose in study 217091 no more than 4 weeks after the last IV dose (administered at week 48 visit of study 213560). The study will include:

- Open-label, 12-week treatment phase.
- Post-treatment follow-up assessments at 8 weeks and 16 weeks after the last dose of SC belimumab

4.2. Scientific Rationale for Study Design

Paediatric SLE is a severe autoimmune disease with multisystem involvement and wide heterogeneity of disease manifestations. It shares similar pathogenesis with adult SLE that includes a complex interaction of genetics, environment, and hormones that leads to immune-tolerance damage, resulting in autoantibody production, inflammation and organ injury. Disease follows an unpredictable course of relapses (flares) and remissions, and there is currently no cure [Moulton, 2017]. Regardless of age of onset or time of diagnosis, Participants with SLE share many immunogenetic and serologic similarities [Aggarwal, 2015; Barron, 1993; Mina, 2013].

Belimumab efficacy in participants with SLE has been established in Chinese adults with SLE in the adult IV study in Northeast Asia (BEL113750) and has been demonstrated to be comparable to efficacy in overseas adults (C1056, C1057, BEL112341) and paediatrics (BEL114055). A clinical pharmacology study 209629, in which PK of both IV and SC in Chinese healthy volunteers were collected, demonstrated that belimumab exposures in Chinese adults after administering 200 mg QW SC and 10 mg/kg Q4W IV are comparable.

In addition, GSK is initiating a study to investigate the effectiveness, safety and PK profile of belimumab IV in Chinese paediatric Participants with SLE (213560). This study was requested as a PAC by CDE during assessment of the NDA to register Benlysta IV for children with SLE aged 5 years and older (Approval letter number 2020S00808/2020S00809).

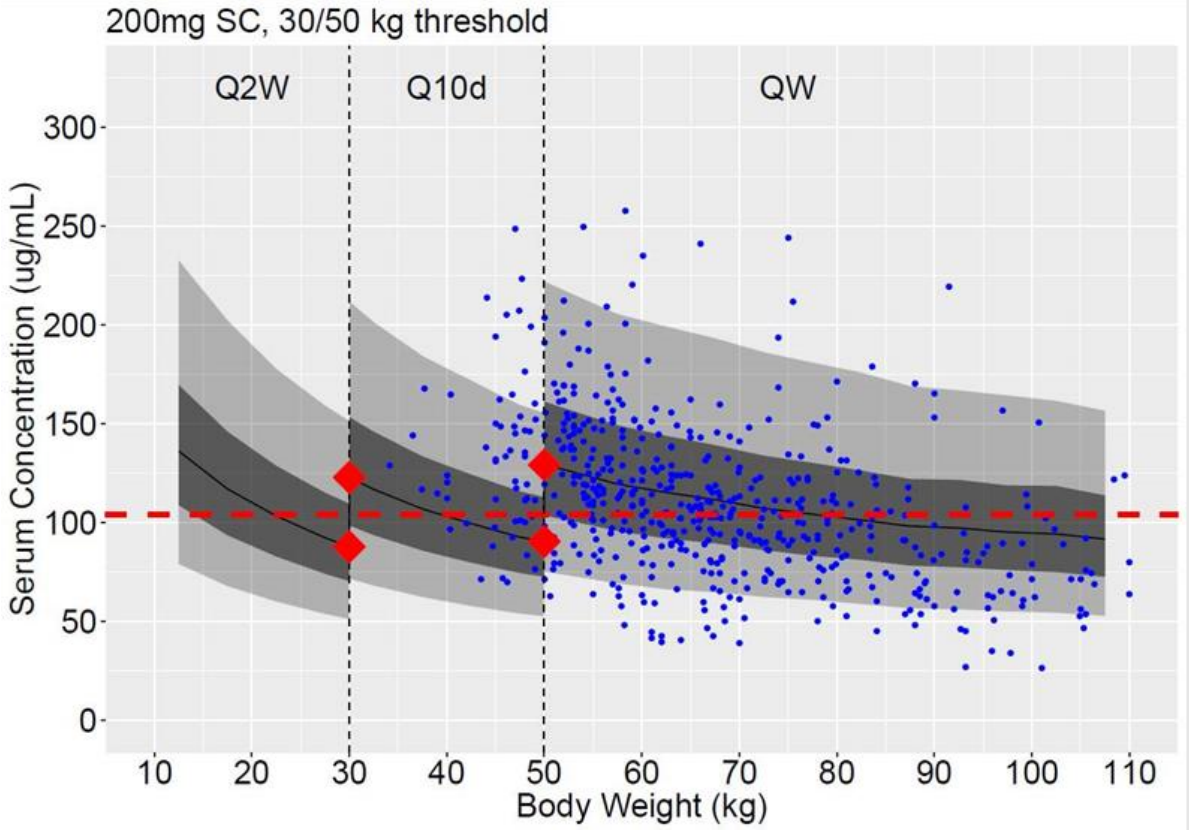
The purpose of this study (217091) is to evaluate the PK characteristics and safety of repeat doses of 200 mg belimumab SC in Chinese paediatric participants by leveraging study 213560, such that paediatric participants completing 48 weeks of IV treatment can switch to SC treatment by joining the SC PK bridging study.

As SLE pathogenesis and disease progression in paediatrics is similar to adults, and the efficacy of belimumab IV 10 mg/kg has been established in Chinese adults, simulation based on the previous population PK model was used to determine the body weight-based dose regimens to be used in study 217091. In order to confirm or optimise the SC dosing regimen for Chinese children with SLE, the population model will be updated when the data from this study are available, and a simulation will be performed to establish comparable SC exposure in Chinese paediatrics with exposure seen in adults following a belimumab IV 10 mg/kg dosing [GSK Document Number 2020N427517_00].

4.3. Justification for Dose

The dose and dosing regimens selected for SC administration in this study are based on calculations intended to achieve a similar average exposure as observed with the weekly 200 mg SC dosing regimen in adult Participants with SLE, estimated from a population PK analysis of SC study data in adults, where the estimated bioavailability (F) was 74.2% without inter-individual variability (IIV) and clearance (CL) was 204 mL/day with 30.2% (CV%) IIV [GSK Document Number 2016N291332_00]. For a fixed belimumab dose (e.g. 200 mg SC), the exposure increases as body weight decreases, as observed in adults and supported by the population PK model developed from the paediatric IV study BEL114055. To accommodate children between the ages of 5 to 17 years, specifically to ensure that participants with lower body weight are not over-exposed, 3 belimumab SC dose groups were proposed and defined by body weight for study 200908 in non-Chinese paediatric participants. Paediatric participants weighing 50 kg or more will receive 200 mg belimumab once a week (QW), as per the recommended dosing regimen in adults. Paediatric participants who weigh between 30 to 50 kg will receive as 200 mg belimumab administered once every ten days (Q10d). Paediatric participants weighing less than 30 kg will receive 200 mg belimumab once every two weeks (Q2W). Belimumab exposure ($C_{ss,\,avg}$) in paediatrics is predicted to be very similar across the three dose groups, as shown in the exposures projected in overseas paediatrics (Figure 1). According to the recommended dose regimen, a higher peak-trough ratio is expected in participants with lower body weight; however, safety is not considered as an issue because even greater PK fluctuation was observed in the participants following 10 mg/kg every four weeks (Q4W) IV belimumab. The effects of body weight on belimumab PK are expected to be the same in overseas participants as in Chinese participants. Therefore, the proposed three-tier dosing regimen used in study 200908, with Q2W dosing for participants <30 kg, Q10d dosing for participants between 30 and <50 kg, and QW dosing for participants ⩾50 kg is considered appropriate for use in this study in Chinese paediatric participants.

Figure 1 Average serum concentrations at steady state versus body weight projected in overseas paediatrics



Pediatric predictions for the median (solid black line), inter-quartile range (dark grey shaded region) and 90% prediction interval (light grey shaded area) are compared with the post-hoc adult estimates (blue points) and the population adult estimate (broken red, 104 ug/mL). The median pediatric concentrations at the 30 mg and 50 mg body weight thresholds are shown (red diamonds 88 and 123 ug/mL at 30 kg, 90 and 129 ug/mL at 50 kg).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed treatment phase (12 weeks) of the study.

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.

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

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Between 5 and 17 years of age inclusive, at the time of informed consent

Type of Participant and Disease Characteristics

2. Chinese paediatric participants with SLE, who have completed 48 weeks treatment in study 213560 and who, in the opinion of the investigator, may benefit from treatment with GSK1550188.

Weight

3. Body weight ≥15kg, at the time of signing the informed consent.

Sex and Contraceptive/Barrier Requirements

4. Male and/or female

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 woman of childbearing potential (WOCBP)

  OR

- Is a WOCBP and is using a contraceptive method that is highly effective, with a failure rate of <1%, as described in 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 have a negative highly sensitive [Appendix 2] pregnancy test (serum or as required by local regulations) within 35 days before the first dose of belimumab.

- 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

5. Participant signs and dates a written age appropriate assent form (in accordance with applicable regulations) and the parent or legal guardian (or emancipated minor) that has the ability to understand the requirements of the study, provides written informed consent (including consent for the use and disclosure of research-related health information) that the participant will comply with the study protocol procedures (including required study visits).

5.2. Exclusion Criteria

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

Medical Conditions

1. Have developed clinical evidence of significant, unstable or uncontrolled, acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases), or experienced an AE in 213560 study that could, in the opinion of the principal investigator, put the participant at undue risk.
2. Have developed any other medical diseases (e.g., cardiopulmonary), laboratory abnormalities, or conditions that, in the opinion of the principal investigator, makes the participant unsuitable for the study.
3. Have an estimated glomerular filtration rate as calculated by Schwartz Formula of less than 30 mL/min.
4. Have an IgA deficiency (IgA level <10 mg/dL).
5. 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 hypoalbuminemia due to lupus nephritis and not related to liver disease or malnutrition.
    b) Any grade proteinuria
    c) 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 alanine transaminase (ALT) and/or aspartate aminotransferase (AST) must be ≤Grade 2.
    d) Stable Grade 3 neutropenia; or stable Grade 3 lymphopenia; or stable Grade 3 leukopenia, due to SLE

Diagnostic Assessments

6. Developing a positive test for HIV antibody after inclusion into 213560, per investigator's discretion according to clinical need.
7. Developing hepatitis B: Serologic evidence of Hepatitis B (HB) infection defined as Hepatitis B surface antigen positive (HBsAg+) OR Hepatitis B core antibody positive (HBcAb+) after inclusion into 213560, per investigator's discretion according to clinical need.
8. Developing a positive test for Hepatitis C antibody after inclusion into 213560, per investigator's discretion according to clinical need.

Prior/Concomitant Therapy

9. Have received a live or live-attenuated vaccine within 30 days of Day 1.

Other Exclusions

10. Are unable or unlikely, in the opinion of the investigator, to administer belimumab by SC injection and have no reliable source to administer the injection.

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.

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. Criteria for Temporarily Delaying Enrolment/Randomization/Administration of Study Intervention

Not Applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

Table 1 Study Intervention(s) Administered

ARM Name	Open label arm
Intervention Name	Belimumab
Type	Biologic
Dose Formulation	SC Injection
Unit Dose Strength(s)	200 mg/mL
Dosage Level(s)	Dose weight ≥50 kg: 200 mg weekly; Dose weight ≥30 kg - <50 kg: 200 mg every 10 days; Dose weight ≥15 kg - <30 kg: 200 mg every 2 weeks
Route of Administration	SC injection (autoinjector)
Sourcing	Provided centrally by the Sponsor
Packaging and Labelling	Belimumab will be provided as an autoinjector
Manufacturer:	**Autoinjector**: The autoinjector components are manufactured by Scandinavian Health Limited (SHL) and assembled with the pre-filled syringe at GSK, Barnard Castle, UK.
Device	Single use autoinjector

6.1.1. Medical Devices

- The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are injection devices: an autoinjector device.

- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

6.2. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm 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. Only participants enrolled in the study may receive study intervention and only authorized 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 labeled storage conditions with access limited to the investigator and authorized 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 autoinjectors are provided in the Study Reference Manual (SRM).
5. 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.
6. 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.
7. The excipients used in the pediatric formulation are safe for administration in the pediatric population participating in the study.

6.3. Measures to Minimize Bias: Randomization and Blinding

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

6.4. Study Intervention Compliance

“Self-administration” is defined as administration of study drug either by the study participant or by the participant’s parent/caregiver. All participants less than 12 years old must have the study drug administered by their parent/caregiver. Whether the study drug is administered by the participant for those 12 years and older will be determined by the participant and his/her parents/caregivers.

Participants or their caregivers should not administer the study agent until they receive proper training in subcutaneous injection technique. Participants and caregivers who do not feel adequately trained with self-injection may return to the site for further training. Participants or caregivers who cannot administer the study drug may have subsequent

subcutaneous injections delivered by qualified study site personnel. Ideally, the injection site should be rotated between the left or right thigh and the abdomen.

6.4.1. Compliance with Subcutaneous Administration of Belimumab

Participants, caregivers or medical staff will be provided with an injection diary (refer to SRM). Dosing compliance must be reviewed with the participant/caregiver/medical staff at each site visit, the injection diary must be reviewed by study site staff and the entries transcribed to the electronic case report form (eCRF). Participants and caregivers are also required to return all used and any malfunctioning autoinjector devices. All unused autoinjectors, including spare devices, must be returned as described in the SRM.

When participants are dosed at the investigative site with belimumab, immediately after the injection, medical staff who inject the drug will complete the injection diary recording the date and time of injection, the injection site and whether or not the entire dose was administered. These injection diary entries will be transcribed into the eCRF by the site staff.

When participants self-administer study treatment(s) at home, immediately after the injection, participants or caregivers will complete the injection diary recording the date and time of injection, the injection site and whether or not the entire dose was administered. Participants must bring their injection diary with them to site visits and compliance with belimumab treatment will be assessed by the site staff through review of the injection diary and transcription of the entries into the eCRF.

A record of the number of belimumab autoinjectors dispensed to and taken by each participant and of unused autoinjectors returned by each participant must be maintained and reconciled with study treatment and compliance records. Used autoinjectors should be placed in a sharps container and returned to the site as described in the SRM. Any returned malfunctioning autoinjectors will be marked to distinguish them from the used autoinjectors (see SRM for details).

6.4.2. Missed Doses

If the participant has not taken the scheduled dose on the due date, the following rules apply:

Weekly dosing – if the scheduled dose has not been administered during the scheduled window the dose should be SKIPPED and dosing should be resumed on the next scheduled date.

10-day dosing – if the scheduled dose has not been administered during the scheduled window it may be administered up to 3 DAYS later. If the dose is not administered within 3 days, the dose should be SKIPPED and dosing should be resumed on the next scheduled date.

2 weekly dosing - if the scheduled dose is not administered during the scheduled window it may be administered up to 7 DAYS later. If the dose is not administered within 7 days the dose should be SKIPPED and dosing should be resumed on the next scheduled date.

The participant should not administer 2 doses on the same day and 2 doses should not be administered to make up for a dose missed.

If a participant misses 2 consecutive doses of belimumab or 3 non-consecutive doses of belimumab, then the Investigator must contact the Medical Monitor to discuss whether the participant should continue in the study (see SRM for details).

6.5. Dose Modification

No dose modifications of belimumab are allowed. Dosing frequency are fixed according the baseline body weight.

Dosing cohort	Dosing frequency
BW ≥50 kg at baseline	Every week
BW ≥30 kg and <50 kg at baseline	Every 10 days
BW ≥ 15 kg and <30 kg at baseline	Every 2 weeks

BW= Body weight

6.6. Continued Access to Study Intervention after the End of the Study

Following the end of treatment at Week 12 or early withdrawal from the study, the participant will follow standard of care for SLE as determined by the investigator.

6.7. 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.

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

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

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs.
- 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

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of screening 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, route and frequency

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

6.8.1. Permitted Medications and Non-Drug Therapies

The investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required during the study unless specifically excluded.

6.8.1.1. Anti-malarials

A new anti-malarial (e.g., hydroxychloroquine, chloroquine, quinacrine) may be started at any time during the study.

The dose of an anti-malarial may be reduced or increased as clinically required at any time during the study.

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

Anti-malarial drugs should be given according to local guidance (see SRM for further details).

NOTE: The use of anti-malarials for either SLE management or malarial prophylaxis is permitted.

6.8.1.2. 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.

Systemic Steroids for SLE-related Disease Activity

The total dose of systemic steroids may be increased or decreased as clinically indicated at any time during the study. 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 American College of Rheumatology (ACR), for steroid dose/duration of induction therapy [Liang, 2004].

Intra-articular Injections of Corticosteroids

Participants may receive intraarticular (IA) corticosteroid injections at any time during the study.

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.

6.8.1.3. Other Immunosuppressive/Immunomodulatory Agents

Starting any new allowable immunosuppressive/immunomodulatory agent is permitted at any time during the study.

The dose of existing immunosuppressive/immunomodulatory agents may be increased or decreased, as clinically required, at any time during the study.

An immunosuppressive/immunomodulatory agent may be replaced with 1 of the abovementioned agents due to documented toxicity or lack of availability. New topical immunosuppressive agents (e.g., eye drops, topical creams) are allowed at any time during the study.

6.8.1.4. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

During the study, 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.

6.8.2. Prohibited Concomitant Therapy

Participants who start prohibited medications or therapies at any time during the study will be considered a 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 213560)

- Anti- Tumor Necrosis Factor (TNF) or anti-IL-6 therapy (e.g., adalimumab, etanercept, infliximab, certolizumab, tocilizumab, golimumab).
- All biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist).
- Janus kinase (JAK) inhibitors.
- 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).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

If study intervention is permanently discontinued, the participant will complete the early withdrawal and follow-up visits as described in Section 8.1.4 and Section 1.3 (SoA) and will be withdrawn from the study.

Participants may be withdrawn from study agent and from the study if at any time:

- It is the wish of the participant (or their legally acceptable representative) for any reason.
- The investigator judges it necessary due to medical reasons.
- Consecutive belimumab injections (Section 6.4.2) or consecutive clinic visits are missed, consult to medical monitor to decide withdrawn or not (Section 8.1.4).

Furthermore, participants will be withdrawn from study agent and subsequently withdrawn from the study if at any time they:

- Become pregnant.
- Receive prohibited therapy
- Experience unacceptable toxicity
- Participate in another interventional clinical trial except Study 213560
- Trigger liver chemistry stopping criteria and/or IgG stopping criteria.

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.

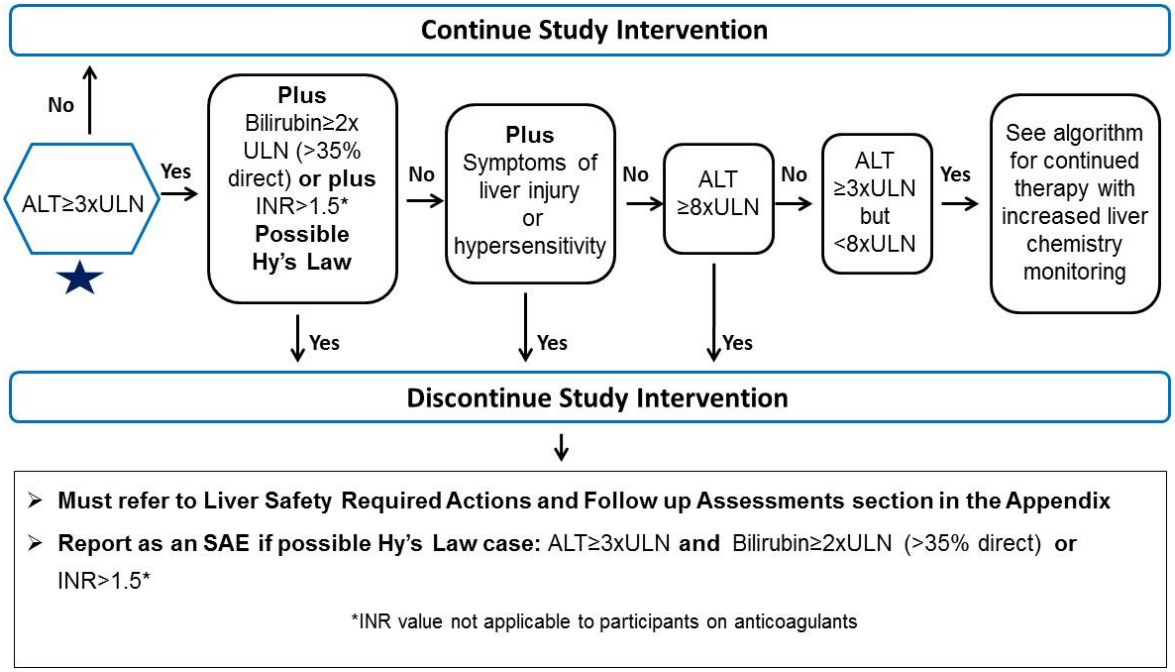
Discontinuation of study intervention for abnormal liver tests is required when:

- 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.

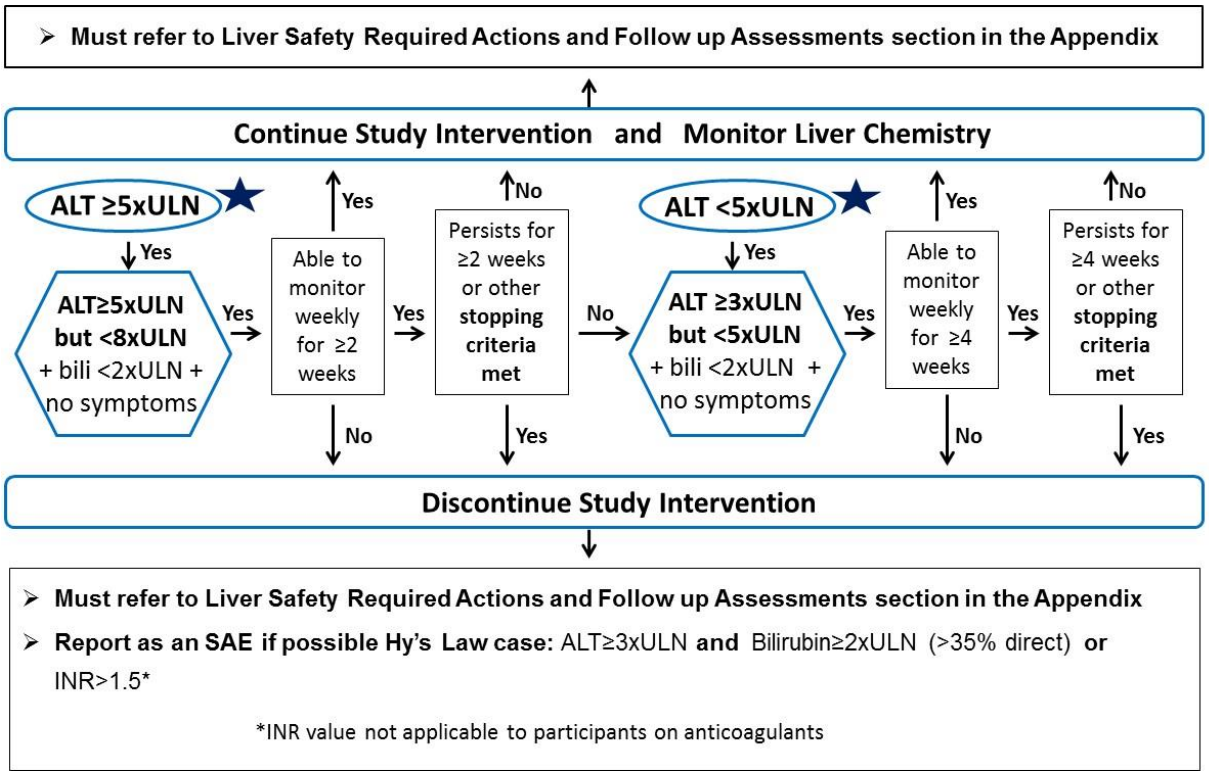
Algorithm A: Phase 3/4 Liver Chemistry Stopping and Increased Monitoring Algorithm



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

Refer to Section 10.6 (Appendix 6) 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 10.6 (Appendix 6) for required Liver Safety Actions and Follow-up Assessments

7.1.2. IgG Stopping Criteria

Any participant who has a Grade 4 IgG level (<250 mg/dL), 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 1.3).

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 are not allowed.

7.2. Participant Discontinuation/Withdrawal from the Study

The legal guardian and the paediatric participant have the right to withdraw permission (consent or assent, respectively) at any time during the study. If the study staff identify any reluctance in the legal guardian or paediatric participant (e.g., signs of verbal or physical dissent) about continued participation in the study, the paediatric participant's continuation in the study should be re-evaluated. The same principles that govern permission/assent/consent also govern its withdrawal.

A participant will be withdrawn from the study for any of the following reasons:

- Withdrawal of consent or assent if applicable (A paediatric participant's dissent should be respected.)
- 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, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA 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 from the study intervention and the study at that time.
- If the participant 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, he/she 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/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 fail 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, counsel the participant on the importance of maintaining the

assigned visit schedule and ascertain whether 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.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized 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.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SoA.

8.1. Screening and Critical Baseline 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 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 (if applicable, in accordance with local regulation). A participant may have treatment assigned when all screening procedures have been completed and eligibility criteria confirmed.

Screening Assessments

Study assessments and procedures will include the following and are detailed in the Schedule of Activities (SOA).

- Demographic information including gender, ethnic origin, race, date and year of birth.
- Medical history.
- Complete physical examination, including height and weight
- Vital signs including temperature, sitting blood pressure, and heart rate
- Confirm classification of SLE disease (based on ACR criteria) by reviewing previously documented clinical records.
- A single 12-lead ECG will be obtained for screening purposes only as outlined in the SoA (see Section 1.3) 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.
- Device Incidents malfunctions
- Blood samples for:
    - Haematology.
    - Modified Chem 20 (non-fasting).
    - Serum pregnancy test - defined as a pre-menarcheal female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue); or a female who has documentation (medical report verification) of a hysterectomy, has both ovaries surgically removed or tubal ligation.
    - PK sampling.
    - Serum immunoglobulin (IgG, IgA and IgM).
- Urine sample for:
    - Routine urinalysis

8.1.1. Baseline Assessments

Procedures at the Baseline Visit are listed in the SOA (Section 1.3). They include clinical assessments and laboratory tests. The interim medical history, including concomitant medications should be reviewed to ensure the participant's eligibility for the study has not changed.

Additional information about these procedures are provided in Section 8.4 (and in the SRM).

8.1.2. Scheduled Visit Assessments

Procedures at the Scheduled Visits are listed in the SoA (Section 1.3). They include clinical assessments, laboratory tests and pharmacokinetics. Time windows are provided for each study visit to allow flexibility in site and participant scheduling. All study visits should occur within the visit window of the scheduled study visit. Additional information about these procedures are provided in Section 8.4 (and in the SRM).

8.1.3. Unscheduled Visit Assessments

Unscheduled visits may be performed for a variety of reasons, including safety. The specific procedures to be performed at an Unscheduled Visit depend on the reason for the Unscheduled Visit. Additional information on the procedures to be performed at an Unscheduled Visit is provided in the SRM.

8.1.4. Early Withdrawal and Follow-up Visit Assessments

Participants who discontinue belimumab treatment and withdraw from the study, are required to complete an Early Withdrawal Visit (within 4 weeks of the decision to withdraw) in addition to the 8-week and 16-week follow-up visit and assessments (see also Section 1.3). If participants are unwilling to return for the 8-week follow-up visit, the early withdrawal visit should be completed at the point of withdrawal and every effort should be made to obtain the results of the home pregnancy assessment, if applicable, and AE collection 16 weeks following the last dose of belimumab.

8.1.5. Missed Study Visits

If a participant misses consecutive study visits, the Investigator should contact the Medical Monitor to discuss whether the participant should continue in the study or be withdrawn (additional guidance is provided in the SRM).

8.2. Efficacy and/or Immunogenicity Assessments

Not applicable

8.3. Safety Assessments

- Adverse Event (including injection-related and hypersensitivity reactions, infections and malignancies) reported throughout the 12-week treatment period and 16-week follow-up.
- Haematological and clinical chemistry parameters (including urinalysis) throughout the 12-week treatment period.
- Vital signs (i.e., pulse rate and systolic and diastolic blood pressure) throughout the 12-week treatment period and 16-week follow-up.
- Physical examination
- 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. Physical Examinations

- A complete physical examination will be conducted at screening, see Section 8.1.
- Abbreviated, symptom-driven examinations will include at a minimum, assessment of the skin, lungs, cardiovascular system, and abdomen (liver and spleen), as well as other relevant organ systems based on participants' symptoms. The abbreviated symptom driven examination will be performed as specified in the SoA (Section 1.3).
- Height and Weight will be measured and recorded as specified in the SoA (Section 1.3). Every effort should be made to maintain a similar practice to measure height and weight throughout the study e.g. shoes on or off, level of clothing to minimize any impact of alteration of these condition on any potential change in height or weight.
- At the discretion of the Investigator, physical and neurological examinations may be performed at unscheduled visits.

8.3.2. Vital Signs

- Systolic and diastolic blood pressure (sitting), heart rate, and body temperature will be measured. Measurements of vital signs will be taken as specified in the SoA (Section 1.3). When belimumab dosing is scheduled to occur in clinic (see Section 1.3), vital signs will be collected pre-dose.
- At the discretion of the Investigator, vital signs may be assessed at unscheduled visits.

8.3.3. Electrocardiograms

- ECG is obtained at screening only, see Section 8.1.

8.3.4. Clinical Safety Laboratory Tests

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- 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 tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during study intervention period.
- Pregnancy testing (urine or serum as required by local regulations) for all females of childbearing potential 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.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) or serious adverse events (SAEs) can be found in Section 10.3.

The definitions of device-related safety events, adverse device effects (ADEs) and serious adverse device effects (SADEs), can be found in Section 10.7. Device deficiencies are covered in Section 8.4.6.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized 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 belimumab.

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.

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

- All AEs and SAEs will be collected from the start of treatment intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions not as AEs.
- 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 Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after 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

- Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

- Study-site staff should instruct the legal guardians and caregivers, on how to report signs and symptoms (e.g., crying and pain) in the individual pediatric participant. They will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhea, sleepiness, variation in the intensity and pattern of crying, etc.). These non-specific symptoms may be the only manifestations of some adverse reaction observed in 5-17 years age participants. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

- Moreover, symptoms that are dependent on participant communication ability (e.g., nausea, pain, mood alterations) in younger or mentally-disabled children could potentially be at risk for under- or mis-reporting.

- These events may or may not have been noted in the participant diary.

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 AESI (i.e., post-injection systemic reactions and hypersensitivity reactions, infections of special interest, malignancies, and depression/suicidality/self-injury), will be followed until the event is resolved, stabilized, 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.

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.
- 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 SAE) 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

- Details of all pregnancies in female participants and, if indicated, will be collected after the start of study intervention and until time period for reporting pregnancies should align with the time period for post-intervention contraception determined in Section 5.1.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the [female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner)] pregnancy. 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.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. 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 in the study will discontinue study intervention or be withdrawn from the study.

8.4.6. Medical Device Deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.3 of the protocol.

8.4.6.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a device deficiency is considered

reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

- Medical device deficiencies and any associated AE/SAEs for associated person (i.e., spouse, caregiver, site staff) will be collected. The associated person will be provided with a safety reporting information and authorisation letter.
- The method of documenting medical device deficiencies is provided in Section 10.7.

8.4.6.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study, and associated persons.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.6.3. Prompt Reporting of Medical Device Deficiencies to the Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The medical device deficiency report form will be sent to the sponsor by email (see SRM for details). If email is unavailable, then paper form should be utilized.
- The sponsor will be the contact for the receipt of device deficiency reports.

8.4.6.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5. Pharmacokinetics

- Blood samples will be collected for measurement of serum concentrations of belimumab as specified in the SoA (Section 1.3) and Table 2. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of belimumab serum concentrations may also be used to help evaluate safety or efficacy questions arising during or after the study.

Table 2 PK visit days and sample times for study participants

Sampling	Body weight ≥50 kg		Body weight ≥30 kg to <50 kg		Body weight ≥15 kg to <30 kg	
	Belimumab 200 mg weekly		Belimumab 200 mg SC every 10 days		Belimumab 200 mg SC every 2 weeks	
	Visit	**Day**	**Visit**	**Time**	**Visit**	**Time**
Additional PK[a]	V1[a]	Screening	V1[a]	Screening	V1[a]	Screening
1	V2[b]	Day1	V2[b]	Day1	V2[b]	Day1
2	V3[c]	Day4±1	V3[c]	Day4±1	V3[c]	Day4±1
3	V4[b, d]	Day8±2	V4[b, d]	Day11±2	V4[b, d]	Day15±2
4	V14[b]	Day78±1	V10[b]	Day71±1	V8[b]	Day71±1
5	V15	Day81±1	V11	Day74±1	V9	Day74±1
6	V16	Day85±2	V12	Day81±2	V10	Day85±2

[a.] For those participants who don't have IV PK samples in study 213560, 3 additional PK samples will be collected within 4 hours, at 7 days (±2 days) and 14 days (±2 days) after last belimumab IV infusion at week 48 of study 213560.

[b.] Samples must be taken pre-dose where the dose is administered on a clinic visit day.

If sampling for PK is missed at Visits 3 and Visit4, the impact will be minimized by attempting to reschedule the missing PK sampling to ensure sufficient precision of PK characterization in Chinese paediatric participants:

- [c.] For the scenario that if the sample collection on visit 3 (Day 4 ± 1 day) was missed, then that PK sample collection should be rescheduled at 3±1 day after any of the next doses.
- [d.] For the scenario that if the sample collection on visit 4 (Day 8/11/15 ± 2 day) was missed, the PK sample collection should be rescheduled to when participants take the next dose and the sample must be taken pre-dose.

Further guidance and information on PK sampling and PK reschedule is provided in SRM.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity parameters are not evaluated in this study.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The study is designed to descriptively evaluate the PK and safety of belimumab plus standard therapy, and as such no formal statistical hypothesis testing is planned.

9.2. Analysis Sets

- The following populations are defined:

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.
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 analyzed.

9.3. Statistical Analyses

9.3.1. General Considerations

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

9.3.2. Primary Endpoint(s)/Estimands(s) Analysis

All pharmacokinetic analyses will be performed on the PK Population. Primary PK analysis will be performed after PK sample collection in all participants has been completed. A population PK analysis will be carried out based on dataset combining PK and demographic data collected in this study (217091) and from studies 213560, BEL114055 and 200908. Individual belimumab exposure parameters ($AUC_{ss\ 0\text{-}\tau}$, $C_{avg,ss}$, $C_{min,ss}$, $C_{max,ss}$) for study 217091 participants will be derived using the population PK model and a statistical summary on these parameters will be performed.

Endpoint	Statistical Analysis Methods
Primary	<u>Endpoints:</u> • Belimumab exposure parameters: $AUC_{ss,\ 0\text{-}\tau}$, $C_{avg,ss}$, $C_{min,ss}$, $C_{max,ss}$ <u>Analysis:</u>

Endpoint	Statistical Analysis Methods
	Descriptive statistics(arithmetic mean, standard deviation of the untransformed data, 95% confidence intervals for the arithmetic mean, median, 25th and 75th percentiles, minimum and maximum, geometric mean, standard deviation of the log-transformed data, 95% confidence intervals for geometric means, between subject coefficient of variation (%CVb, if applicable) will be used to summarize the belimumab exposure parameters: $AUC_{ss,\ 0\text{-}\tau}$, $C_{avg,ss}$, $C_{min,ss}$, $C_{max,ss}$

Belimumab exposure parameters ($AUC_{ss,\ 0\text{-}\tau}$,$C_{avg,ss}$, $C_{min,ss}$, $C_{max,ss}$) estimated for all subjects of this study will be summarised and reported in the clinical study report (CSR) of this study. The belimumab exposure parameters will be estimated using a population PK approach based on the integrated dataset including the PK and demographic information from study 213560, 217091, 200908, BEL114055, and may also include PK from other relevant studies in adults. The detailed information about the methods, the results e.g. parameter estimation, goodness of fit, etc. will be reported separately in a model report.

Further details on the population PK analysis will be discussed in the population PK reporting and analysis plan.

9.3.3. Secondary Endpoint Analysis

All safety analyses will be performed on the ITT population.

Endpoint	Statistical Analysis Methods
Secondary (Safety)	Endpoints: Occurrence of adverse events, serious adverse events and adverse events of special interest through Week12. Analysis: Descriptive statistics (frequency and percentage) will be used to summarize AEs, SAEs, and AESIs. The frequency of AEs will be tabulated by MedDRA SOC and preferred term (PT).

9.4. Interim Analysis

No formal interim analyses are planned.

9.5. Sample Size Determination

There are no formal calculations of power for this study. The sample size justification for study 217091 is based on the precision in the estimate of the geometric mean of Cavg,ss, over all study participants. The coefficient of variation (CV) for between-subject variability in Cavg,ss was approximated to 35.5%, equal to the variability evaluated in overseas children receiving belimumab IV in study BEL114054 [Dimelow, 2020], on the

basis that bioavailability for SC dosing is similar in all subjects and does not significantly increase variability in exposure.

Cavg,ss is expected to be log-normally distributed and the 95% confidence interval (CI) relative to the geometric mean is given by $\exp(\pm t_{97.5,\ N-1} \times sd/\sqrt{N})$, where $t_{97.5,\ N-1}$ is the 97.5^{th} percentile of the t-distribution with N-1 degrees of freedom, sd is the standard deviation in the logarithm of Cavg,ss equal to 0.345 for 35.5% CV, and N is the number of subjects.

For N of 14, the 95% confidence interval in Cavg,ss relative to the geometric mean is 82% to 122%. The 95% CI therefore lies within 22% of the point estimate for Cavg and this level of precision is considered adequate to characterise belimumab exposure in Chinese children receiving belimumab SC.

Considering the withdrawal rate in the previous and ongoing Benlysta paediatric studies in overseas and China, the withdrawal rate in the current study is estimated to be 20%. To account for a 20% withdrawal rate, the total sample size is 17.

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 Organizations of Medical Sciences (CIOMS) international ethical guidelines

  Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines

  Applicable laws and regulations

- The protocol, protocol amendments, ICF, IB, 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.

- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations,
  - The investigator will be responsible for reporting cases of suspected child abuse and/or neglect according to local medical association (e.g., American Academy of Pediatrics [AAP], EU Academy of Pediatrics [EAP]) 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 and Assent Process

- The investigator, or a person designated by the investigator, will provide the legal guardian (refer to Abbreviations and Definitions) with the written ICF and the participant with the assent if applicable. They must be informed that participation is voluntary. The legal guardian will be required to sign written consent, and the participant if applicable will be required to sign written 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 center after the nature of the study has been fully explained and before performance of any study-related activity.
- Assent requirements for pediatric participants may vary across regions and countries; local regulations should be followed as appropriate.
- 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 centrer.
- The medical record must include a statement that written informed consent from the legal guardian and assent from the pediatric participant (if deemed appropriate by local ethics review or local regulations) were obtained before the participant was enrolled in the study and the date the written consent and assent were obtained. The medical record should describe how the clinical investigator determined that the person signing the ICF was the participant's legal guardian. The authorized person obtaining the informed consent must also sign the ICF and assent form attesting that the pediatric participant did not show signs of dissent particularly in those studies including toddlers and small children; it should be written in language appropriate to the child's developmental and functional status.
- Participants and their legally authorised representative (parent/guardian) must be reconsented and re-assented to the most current version of the ICF(s) during their participation in the study.
- Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their legal guardian still wants them to participate.
- 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.
- As appropriate, participants may be given the opportunity to meet privately with a member of the site staff to ask confidential questions and to decline assent for confidential reasons, which, at their request, would not be shared with their legal guardian, unless required by local law.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- There will be no attempt to recontact the participant at adulthood. However, the participant retains the right to withdraw assent/consent for storage of samples unless specified, e.g., if adolescent becomes legal age during the study, they should be reconsented.
- Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent/assent for their samples to be stored for research.
- If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.

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 authorized 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 all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants' received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.

- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs 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.
- Guidance on completion of CRFs will be provided in eCRF guideline.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- 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 including definition of study critical data items and processes (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. Detailed information about study data collection and management process including systems used can be found in the study equivalent Contract Research Organization (CRO) document].
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- 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 and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized 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.

10.1.8. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- 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 organization(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 subject 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 multicenter 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 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.
- 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 Red blood cell (RBC) Count Haemoglobin Haematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Calcium	Potassium	Aspartate Aminotransferase	Total bilirubin

Laboratory Assessments	Parameters			
			(AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	
	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/glomerular filtration rate (Schwartz[3])
Routine Urinalysis	• pH, glucose, protein, blood, ketones, occult blood by dipstick • Microscopic examination			
Urine Pregnancy[2]	• Urine pregnancy if applicable			
Immunoglobulins	• Serum immunoglobulin isotypes: IgG, IgM, IgA			
PK	• Blood collection			
Other Screening Tests	• 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)			

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 7.1.1 and Appendix 6. 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. 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, LLLN = Lower Limit of Normal
**Lymphopenia calculated from Common Terminology Criteria for Adverse Events (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)

CHEMISTRIES	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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)

CHEMISTRIES (continued)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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)

	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
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

FEV = Forced expiratory volume

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: AEs and SAEs: 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 unfavorable 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
For efficacy studies, include the penultimate bullet, and for nonefficacy studies involving marketed products in established indications, include the final bullet. • Any abnormal laboratory test results (hematology, 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 condition 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 intervention- intervention 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.

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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (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 hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention 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.
- 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 required form.
- 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 one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 submitted documents. • 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) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • 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 Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool 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.

SAE Reporting to GSK via Paper Data Collection Tool
• Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

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

10.5. Appendix 5: Genetics

Not applicable

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart/Rechallenge Guidelines

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

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	ALT ≥ 5xULN but <8xULN **and** cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN **and** cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• 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.	• 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

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	• Obtain complete blood count with differential to assess eosinophilia • 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.

10.7. Appendix 7: Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.7.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event **that:**
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. 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. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect

A Medical Device SAE is any serious adverse event **that:**
d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.7.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to in lieu of completion of the AE/SAE/device deficiency form. • There may be instances when copies of medical records for certain cases are requested by medical monitor. 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 the medical monitor.

AE, SAE and Device Deficiency Recording

- 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.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Other measures to evaluate AEs and SAEs may be used (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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.

Assessment of Causality
• The investigator will also consult the IB, in his/her assessment. • For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency 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/SAE/device deficiency
• 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/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed form. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.7.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool
• The primary mechanism for reporting an 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 table) 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. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

SAE Reporting to GSK via an Electronic Data Collection Tool
• 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 GSK medical monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

10.7.6. Reporting of SADEs

SADE Reporting to GSK
NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Refer to the paper medical device deficiency report form for details on transmission of this information to the sponsor.

10.7.7. Reporting of Medical Device Deficiencies for Associated Person

Reporting to GSK
If an Associated Person (i.e. e.g. spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the authorization to contact physician letter. If follow up information is required, authorization to contact physician (or other licensed medical practitioner' must be signed to obtain consent.

Reporting to GSK
• Medical device deficiencies that are not related to an AE or SAE should be reported via email to gsk-rd.complaints@gsk.com, using the medical device deficiency report form. • If the medical device deficiency is related to a non-serious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to gsk-rd.complaints@gsk.com only. • If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours, to **both** uk.gsk-rd-gcsp-ctsm-admin@gsk.com (or fax +44(0)20 8754 7822) **and** gsk-rd.complaints@gsk.com. The associated SAE form should also be reported to uk.gsk-rd-gcsp-ctsm-admin@gsk.com (or fax +44(0)20 8754 7822). • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for Medical Device Deficiency reporting can be found in the medical device deficiency report form.

10.8. Appendix 8: Protocol amendment history

Amendment 01:24 Jan 2024

Overall Rationale for the amendment:

The main purpose of this protocol amendment is to add an additional two PK sampling points after the last IV dose of study 213560 for the non-PK participants of that study who then enrol into the SC study (217091) in order to better characterise the PK parameter estimation and precision.

The study sample size has been increased from 14 to 17 to take into account an estimated participant withdrawal rate of 20%.

Further guidance is provided for the rescheduling timeframe for PK sampling visits that have been missed to ensure sufficient precision of PK characterization.

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

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis Overall Design Number of Participants	Updated sample size number from 14 to 17. Updated wording in the 1st sentence of "Note" as below, Enrolled means a participant's (if applicable) and their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and screening.	Enlarged sample size to account for estimated 20% withdrawal rate. According to China regulations, not every paediatric participant needs to sign the ICF but their legally acceptable representative's signing ICF is mandatory.
1.2 Schema	Added "Note" as below, Note: For those participants who don't have IV PK samples in study 213560, 3 additional PK samples will be collected within 4 hours, at 7days (±2 days) and 14 days (±2 days) after last belimumab IV infusion at week 48 of study 213560.	To mitigate the risk of insufficient precision of bioavailability in participants enrolled from non-PK subjects in study 213560 additional PK sampling points have been included.

1.3 Schedule of Activities (SoA)	Shorten visit window from ±2 days to ±1 day on V3 for each cohort of Body Weight (BW). Shorten visit window from ±2 days to ±1 day on V14 and V15 in cohort of BW ⩾50 kg, V10 and V11 in cohort of BW ⩾30 kg and <50 kg, V8 and V9 in cohort of BW ⩾15 kg and <30 kg respectively.	To minimize the fluctuation of the sampling time and avoid possible overlap of study visits.
	Increased height recording in each visit with Laboratory Assessments	For eGFR calculation in safety visits.
	Deleted superscript 8 (samples must be taken pre-dose) for PK sampling visits as below: BW ⩾50 kg at V16 BW ⩾30 kg and <50 kg at V12 BW ⩾15 kg and <30 kg at V10	Corrected to account for no dose administration at this visit.
	Updated information in footnote 7 as below: For those participants who don't have IV PK samples in study 213560, 3 additional PK samples will be collected within 4 hours, at 7 days (±2 days) and 14 days (±2 days) after last belimumab IV infusion at week 48 of study 213560.	To mitigate the risk of insufficient precision of bioavailability in participants enrolled from non-PK subjects in study 213560.
	Deleted "(Day1 and Week1)" in footnote 9.	To reflect that depending on the body weight cohort, this is not always at Week 1.
	Added footnote 10 and 11 for PK sampling reschedule as below, 10. If the PK sample collection on visit 3 was missed, then that PK sample collection should be rescheduled at 3 ±1 day after any of the next doses.	To help investigator further understand rescheduling the missing PK sampling.

	11. If the PK sample collection on visit 4 was missed, then that PK sample collection should be rescheduled to when participants taken the next dose and sample must be taken pre-dose.	
4.1 Overall Design	Updated sample size number from 14 to 17.	Enlarged 20% of sample size to mitigate the risk of 20% drop-out rate.
6.8.2 Prohibited Concomitant Therapy	Added "Janus kinase (JAK) inhibitors" as prohibited concomitant therapy.	JAK inhibitors are more commonly used as target therapy in SLE in China, however there is no safety evidence on JAK inhibitors combine with belimumab. Add JAK inhibitors as prohibited concomitant therapy to reduce drug interactions.
8.1. Screening and Critical Baseline Assessments	Updated the 2nd sentence of "Informed Consent" as below, The participant will provide their assent to participate in the study at the same time (if applicable, in accordance with local regulation).	According to China regulations and GCP, not every paediatric participant needs to sign the ICF.
8.5 Pharmacokinetics	Added a new table (table 2) and footnotes to summarize the PK visit days and sample times.	To help investigator understand the PK sampling points more clearly.
9.5. Sample Size Determination	Added new wording as below, Considering the withdrawal rate in the previous and ongoing Benlysta paediatric studies in overseas and China, the withdrawal rate in the current study is estimated to be 20%. To account for a 20% withdrawal rate, the total sample size is 17.	Previous sample size did not take withdrawal rate into consideration.
10.2. Appendix 2: Clinical Laboratory Tests	Updated the table number from 2 to 3.	Updated the table number for adding a new Table 2 in Section 8.5

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