TITLE PAGE

Protocol Title: A Multi-Center, Open-Label Trial to Evaluate the Pharmacokinetics, Safety, and Pharmacodynamics of Subcutaneously Administered Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Participants with Systemic Lupus Erythematosus (SLE)

Protocol Number: 200908/Amendment 04

Compound Number:	GSK1550188

Study Phase: Phase 2

Short Title: Open label study of Subcutaneous Belimumab in Pediatric Participants with Systemic Lupus Erythematosus (SLE)

Acronym: PLUTO-SC

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 4	14 Dec 202214 Dec 2022	TMF-15202454
Amendment 3	14-Jul-2021	TMF-13827130
Amendment 2	24-Apr-2020	2018N373284_03
Amendment 1/GER-1	22-Nov-2019	2018N373284_02
Amendment 1	24-Jul-2019	2018N373284_01
Original protocol (00)	29-Apr-2019	2018N373284_00

Amendment 4 : 14 Dec 2022

Overall Rationale for the Amendment:

The purpose of this amendment is to accurately reflect the end of study definition as the last subject last visit occurring during the optional access extension phase vs. Part A and Part B of the study.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 4.4, End of Study Definition	Revised end of study definition from last participant in Part A and Part B of the study to last participant in optional access extension phase.	To accurately reflect last subject last visit occurring during the optional access extension phase.
Section 6.7, Intervention after the End of the Study (previous)	Modified Section heading to: 6.7. Intervention after completion of Part A and Part B	To accurately reflect last subject last visit occurring during the optional access extension phase.
Appendix 10.3.4, Reporting of SAE to GSK	Revised statement as follows: • After Part B of the study is completed at a given site, the electronic data collection tool will be ~~taken off line~~locked to prevent the entry of new data or changes to existing data.	Due to the end of study definition being revised to last participant in the optional access extension phase.
Appendix 10.11, Abbreviations and Trademarks	Removed GSK from the list of abbreviations	Due to corporate rebranding

Section # and Name	Description of Change	Brief Rationale
Global	Replaced GlaxoSmithKline with GSK throughout the document.	Due to corporate rebranding

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Multi-Center, Open-Label Trial to Evaluate the Pharmacokinetics, Safety, and Pharmacodynamics of Subcutaneously Administered Belimumab, a Human Monoclonal Anti-BLyS Antibody, Plus Standard Therapy in Pediatric Participants with Systemic Lupus Erythematosus (SLE)

Short Title: Open label Study of Subcutaneous Belimumab in Pediatric Participants with Systemic Lupus Erythematosus (SLE)

Rationale: The purpose of this study is to evaluate the pharmacokinetics (PK), safety, and pharmacodynamics (PD) of repeat doses of 200 mg belimumab administered subcutaneously (SC) in pediatric participants 5 to 17 years of age with systemic lupus erythematosus (SLE) on a background of standard of care therapy. This bridging PK study is part of an extrapolation strategy to support the use of SC belimumab in pediatric SLE patients, based on the completed adult SLE study with SC belimumab and the pediatric SLE study with IV belimumab, and is a component of a post-approval commitment to EMA (EMA-000520-PIP02-13-M01) and FDA (postmarketing requirement 3239-1 under BLA 761043**).**

Objectives and Endpoints:

Objective	Endpoint
Primary - Pharmacokinetics	
• To characterize the PK profile of belimumab 200 mg SC in pediatric SLE participants.	• Observed belimumab concentrations at Week 12. • Steady-state PK parameters: Cavg (AUC), Cmax, Cmin (based on population PK estimates).
Secondary - Safety	
• To evaluate the safety and tolerability of belimumab 200 mg SC in pediatric SLE participants.	• Incidence of adverse events, serious adverse events and adverse events of special interest through Week 52.
Secondary - Biomarkers	
• To characterize the pharmacodynamic profile of SC belimumab 200 mg SC in pediatric SLE participants.	• Change from baseline in biomarkers (C3/C4, anti-dsDNA, B cell subsets, and immunoglobulins) at Weeks 12 and 52.
Other - Efficacy	
• To characterize the impact on disease activity of belimumab 200 mg SC in pediatric SLE participants	• Percent of subjects with a ≥ 4 point reduction from baseline in SELENA SLEDAI at Weeks 12 and 52.

Overall Design:

This is a single arm, multi-center open-label study to evaluate the PK, safety, and PD of SC belimumab plus background standard therapy in approximately 28 pediatric participants ages 5 to 17 years of age and weighing ≥15 kg with active SLE. The study will include:

- Part A: Open-label, 12-week treatment phase.
- Part B: Optional 40-week open-label continuation phase for any participant who completes Part A.
- Post-treatment follow-up assessments at 8 and 16 weeks after the last dose of SC belimumab.
- Optional Access Extension Phase: Optional post-Week 52 extension phase exclusively for eligible participants who complete Part B (e.g., participants from countries where the IV formulation is not approved for pediatric use; or participants in whom IV Benlysta is not suitable due to medical reasons or significant logistical challenges).

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

Number of Participants:

It is expected that 36 participants will need to be screened to enroll approximately 28 participants aiming to achieve 24 evaluable participants at Week 12. Enrollment and study withdrawals will be closely monitored and if there is an impact on continuation of participants in the study due to the Coronavirus SARS-CoV-2 (COVID-19) pandemic, more than 36 participants may be screened, and more than 28 may need to be enrolled, to ensure the ability to achieve the evaluable target at Week 12.

Intervention Groups and Duration:

The total maximum duration of study participation (Part A and Part B) for each participant is 73 weeks (screening:5 weeks, treatment: up to 52 weeks [12 weeks Part A plus 40 weeks extension phase] and follow-up: 16 weeks).

Cohort 1 will include participants ≥50 kg body weight, Cohort 2 will include participants ≥30 to <50 kg body weight and Cohort 3 will include participants <30 kg body weight at baseline. In Part A Cohort 1 will receive weekly doses of belimumab 200 mg SC, Cohort 2 will receive belimumab 200 mg SC every 10 days and Cohort 3 will receive belimumab 200 mg SC every 2 weeks.

In Part B, the dosing frequency may change according to pre-defined criteria based on changes in body weight of the participant.

The optional access extension phase is to provide a mechanism for continued access to belimumab SC from Week 52 onwards and is exclusive only for eligible participants who complete Part B of the study (e.g., participants from countries where the IV formulation

is not approved for pediatric use; or participants in whom IV Benlysta is not suitable due to medical reasons or significant logistical challenges for full eligibility criteria). The duration of this optional access extension phase will depend on age of the participants and the conditions for eligibility. During the access extension phase, the dosing frequency may change based on changes in body weight of the participant. Participants who are enrolled into the optional access extension phase will be withdrawn from treatment if they reach the age of 18 years, if Belimumab SC or IV becomes licensed and commercially available for pediatric use in the participant's country.

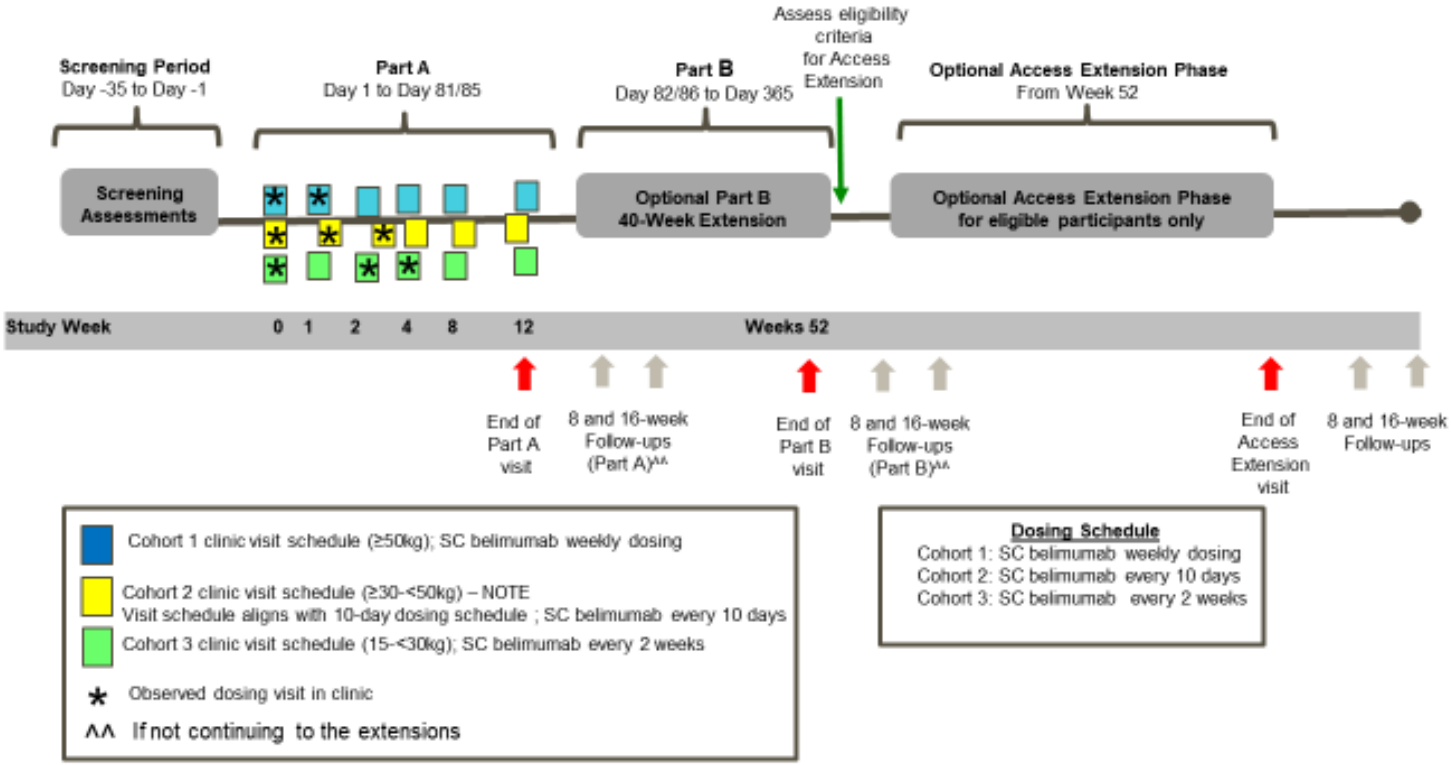
Safety Review Team (SRT)

An internal GSK Safety Review Team will monitor and perform in-stream review of safety data throughout Part A and Part B of the study. The optional access extension phase will not be part of this in-stream review.

Pharmacokinetic Review Team (PRT)

An internal GSK Pharmacokinetic Review Team will review in-stream PK data during Part A and Part B and if necessary recommend dose adjustments.

1.2. Schema


Screening Period
Day -35 to Day -1
Part A
Day 1 to Day 81/85
Part B
Day 82/86 to Day 365
Assess eligibility criteria for Access Extension
Optional Access Extension Phase
From Week 52
Screening Assessments
Optional Part B 40-Week Extension
Optional Access Extension Phase for eligible participants only
Study Week
0 1 2 4 8 12
Weeks 52
End of Part A visit
8 and 16-week Follow-ups (Part A)^^
End of Part B visit
8 and 16-week Follow-ups (Part B)^^
End of Access Extension visit
8 and 16-week Follow-ups
Cohort 1 clinic visit schedule (≥50kg); SC belimumab weekly dosing
Cohort 2 clinic visit schedule (≥30-<50kg) – NOTE
Visit schedule aligns with 10-day dosing schedule ; SC belimumab every 10 days
Cohort 3 clinic visit schedule (15-<30kg); SC belimumab every 2 weeks
* Observed dosing visit in clinic
^^ If not continuing to the extensions
Dosing Schedule
Cohort 1: SC belimumab weekly dosing
Cohort 2: SC belimumab every 10 days
Cohort 3: SC belimumab every 2 weeks

1.3. Schedule of Activities (SoA)

1.3.1. SOA 1.Part A - Cohort 1 (body weight ≥50 kg at baseline) and Cohort 3 (body weight <30 kg at baseline)

Note: In Part B and in the optional accesss extension phase, participants may need to switch dosing frequency according to changes in body weight (See Section 6.6 Dose Modification)

Procedure	Part A - Subcutaneous PK/PD Safety [Cohort 1 and Cohort 3] Screening to Day 85 (Week -5 to 12)								
	Screening and eligibility -35 days[10]	Treatment Period						Follow-Up Period[1,2]	
Study Day		Day 1	Day 8 ±2 days	Day 15 ±2 days	Day 29 ±2 days	Day 57 ±2 days	Day 85 ±2 days	8-Week Follow-up ±7 days[1]	16-Week Follow-up ±7 days[1,2]
Study Week		Wk 0	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12/EW[1]		
Written Informed Consent	X								
Demography	X								
Medical History	X								
Inclusion/Exclusion Criteria	X	X							
SELENA SLEDAI	X	X					X		
Vital Signs	X	X	X	X	X	X	X	X	
Weight + Height	X	X	x	x	X	X	X	X	
12-Lead ECG	X								
Physical Examination[3]	X	X	X	X	X	X	X	X	

Procedure	Part A - Subcutaneous PK/PD Safety [Cohort 1 and Cohort 3] Screening to Day 85 (Week -5 to 12)								
	Screening and eligibility -35 days[10]	Treatment Period						Follow-Up Period[1,2]	
Study Day		Day 1	Day 8 ±2 days	Day 15 ±2 days	Day 29 ±2 days	Day 57 ±2 days	Day 85 ±2 days	8-Week Follow-up ±7 days[1]	16-Week Follow-up ±7 days[1,2]
Study Week		Wk 0	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12/EW[1]		
Adverse Events[4]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Device incidents/malfunctions		X	X	X	X	X	X		
Laboratory Assessments									
Hematology	X	X			X	X	X	X	
Urinalysis	X	X			X	X	X	X	
Chemistry	X	X			X	X	X	X	
Spot Urine (protein:creatinine)	X	X			X	X	X	X	
Pregnancy Test[5]	X	X	X	X	X	X	X	X	X
BLyS Protein[8]		X							
PT/PTT	X								
C3/C4, CRP[8]	X	X			X	X	X	X	

Procedure	Part A - Subcutaneous PK/PD Safety [Cohort 1 and Cohort 3] Screening to Day 85 (Week -5 to 12)								
	Screening and eligibility -35 days[10]	Treatment Period						Follow-Up Period[1,2]	
Study Day		Day 1	Day 8 ±2 days	Day 15 ±2 days	Day 29 ±2 days	Day 57 ±2 days	Day 85 ±2 days	8-Week Follow-up ±7 days[1]	16-Week Follow-up ±7 days[1,2]
Study Week		Wk 0	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12/EW[1]		
B-Cells[8]		X		X	X	X	X	X	
Anti-dsDNA, ANA[8]	X	X			X	X	X	X	
Immunogenicity		X			X		X	X	
IgA, IgG and IgM[8]	X	X			X	X	X	X	
Hepatitis B, Hepatitis C, HIV	X								
Belimumab Administration and PK Sampling									
Training - Use of Autoinjector	X	X							
In Clinic Administration of Belimumab (**Cohort 1** ≥50 kg)[6]		X	X	X	X	X	X[9]		
In Clinic Administration of Belimumab (**Cohort 3** <30 kg)[7]		X		X	X	X	X[9]		
PK Sampling[8]			X	X	X	X	X	X	

1. 8- and 16-week follow-up is required for participants who withdraw from study treatment prior to the end of Part A and for participants who complete Part A but do not wish to continue into Part B. For participants who withdraw from treatment prior to Week 12, in addition to the 8- and 16-week follow-up visit and assessments, an early withdrawal visit (EW) should be completed. The EW visit requires identical assessments and procedures to the Week 12 visit.
2. 16-week follow-up requires a phone call to collect AEs, concomitant medications and the results of home urine pregnancy test (if applicable) for female participants. NOTE: the 16-week follow-up may be performed at a clinic visit per local requirement.
3. Full Physical Examination is required at screening (Section 8.1). An abbreviated/symptom-driven exam can be done thereafter.
4. Please refer to Section 8.9.1.for the time period for collection of AEs/SAEs
5. 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.
6. Cohort 1 (≥50 kg at baseline): Study drug to be administered weekly in Part A. Administration in clinic is mandated where specified in the Schedule of Activities (SOA), otherwise at home self-administration is encouraged (see Section 6.4). For the first 2 doses (Day 1 and Week 0) participants must be observed for 3h post belimumab injection (see Section 6.4).
7. Cohort 3 (<30 kg at baseline): Study drug to be administered every 2 weeks in Part A. Administration in clinic is mandated where specified in the SOA, otherwise at home self-administration is encouraged (see Section 6.4). For the first 2 doses (Day 1 and Week 1), participants must be observed for 3h post belimumab injection (see Section 6.4).
8. Samples must be taken pre-dose.
9. Dosing only occurs for participants who elect to continue in Part B.
10. Participants in Cohort 3 (<30 kg) will have the screening blood collection and testing split across 2 visits separated by at least 2 weeks and between the 2nd screening and Day 1 visits to ensure the blood volume collected remains within local guidelines. Note: This may also apply to particpants ≥30kg according to local guidelines.

1.3.2. SOA 2 Part A Cohort 2 (Body weight ≥30 kg - <50 kg at baseline)

Note: In Part B and in the optional access extension phase, participants may need to switch dosing frequency according to changes in body weight (See Section 6.6 Dose Modification)

Procedure	Part A - Subcutaneous PK/PD Safety [Cohort 2] Screening to Day 81 (Week -5 to 11[9])								
	Screening and eligibility -35 days[10]	Treatment Period						Follow-Up Period[1,2]	
Study Day		Day 1	Day 11 ±2 days	Day 21 ±2 days	Day 31 ±2 days	Day 61 ±2 days	Day 81[1] ±2 days	8-Week Follow-up ±7 days[1]	16-Week Follow-up ±7 days[1,2]
Written Informed Consent	X								
Demography	X								
Medical History	X								
Inclusion/Exclusion Criteria	X	X							
SELENA SLEDAI	X	X					X		
Vital Signs	X	X	X	X	X	X	X	X	
Weight + Height	X	X	x	x	X	X	X	X	
12-Lead ECG	X								
Physical Examination[3]	X	X	X	X	X	X	X	X	
Adverse Events[4]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X

Procedure	Part A - Subcutaneous PK/PD Safety [Cohort 2] Screening to Day 81 (Week -5 to 11[9])								
	Screening and eligibility -35 days[10]	Treatment Period						Follow-Up Period[1,2]	
Study Day		Day 1	Day 11 ±2 days	Day 21 ±2 days	Day 31 ±2 days	Day 61 ±2 days	Day 81[1] ±2 days	8-Week Follow-up ±7 days[1]	16-Week Follow-up ±7 days[1,2]
Device incidents/malfunctions		X	X	X	X	X	X		
Laboratory Assessment									
Hematology	X	X			X	X	X	X	
Urinalysis	X	X			X	X	X	X	
Chemistry	X	X			X	X	X	X	
Spot Urine (protein:creatinine)	X	X			X	X	X	X	
Pregnancy Test[5]	X	X	X	X	X	X	X	X	X
BLyS Protein[8]		X							
PT/PTT	X								
C3/C4, CRP[8]	X	X			X	X	X	X	
B-Cells[8]		X		X	X	X	X	X	
Anti-dsDNA, ANA[8]	X	X			X	X	X	X	
Immunogenicity		X			X		X	X	

Procedure	Part A - Subcutaneous PK/PD Safety [Cohort 2] Screening to Day 81 (Week -5 to 11[9])								
	Screening and eligibility -35 days[10]	Treatment Period						Follow-Up Period[1,2]	
Study Day		Day 1	Day 11 ±2 days	Day 21 ±2 days	Day 31 ±2 days	Day 61 ±2 days	Day 81[1] ±2 days	8-Week Follow-up ±7 days[1]	16-Week Follow-up ±7 days[1,2]
IgA, IgG and IgM[8]	X	X			X	X	X	X	
Hepatitis B, Hepatitis C, HIV	X								
Belimumab Administration and PK Sampling									
Training - Use of Autoinjector	X	X							
In Clinic Administration of Belimumab (**Cohort 2** ≥30 - <50kg)[6]		X	X	X	x	x	X[7]		
PK Sampling[8]			X	X	X	X	X	X	

1. 8- and 16-week follow-up is required for participants who withdraw from study treatment prior to the end of Part A and for participants who complete Part A but do not wish to continue into Part B. For participants who withdraw from treatment prior to Day 81 (Week 11), in addition to the 8- and 16-week follow-up visit and assessments, an early withdrawal visit (EW) should be completed. The EW visit requires identical assessments and procedures to the Day 81 visit.
2. 16-week follow-up requires a phone call to collect AEs, concomitant medications and the results of home urine pregnancy test (if applicable) for female participants. NOTE – 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 8.8.1
4. Adverse Event collection: Please refer to Section 8.9.1
5. 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.
6. Cohort 2 (≥30 - <50 kg): Study drug to be administered every 10 days in Part A (see Section 6.4). Administration in clinic is mandated where specified in the Schedule of Activities (SOA), otherwise at home self-administration is encouraged (see Section 6.4). For the first 2 doses (Day 1 and Day 11) participants must be observed for 3h post belimumab injection (see Section 6.4). Note the visit schedule for Cohort 2 participants differs from Cohorts 1 and 3 but aligns with dosing schedule without adding additional visits.
7. Dosing occurs only for participants who elect to continue in Part B.
8. Samples must be taken pre-dose where the dose is administered on a clinic visit day.

9. Note – Study weeks are not shown for Cohort 2 as the weeks for this cohort do not align with those for Cohorts 1 and 3 for all visits. The visits for Cohort 2 should be planned according to the Study Days shown in the header.
10. Participants in Cohort 2 (≥30-<50 kg) may have the screening blood collection and testing split across 2 visits separated by at least 2 weeks and between the 2nd screening and Day 1 visits to ensure the blood volume collected remains within local guidelines.

1.3.3. SOA 3 Part B - Applies to all participants who enter Part B

Note: Participants may need to switch dosing frequency according to change in body weight (See Section 6.6 Dose Modification)

Procedure	Part B - Optional Treatment Extension - Days 86-365 (Weeks 13-52) [All participants]								
	Treatment Period							Follow-Up Period	
Study Day	Day 113 ±7 days	Day 141 ±7 days	Day 169 ±7 days	Day 211 ±7 days	Day 253 ±7days	Day 309 ±7days	Day 365 ±7 days	8-Week Follow-up ±7 days[1]	16-Week Follow-up ±7days [1,2]
Study Week	Wk 16	Wk 20	Wk 24	Wk 30	Wk 36	Wk 44	Wk 52/EW[1]	Wk 60	Wk 68[2]
SELENA SLEDAI							X		
Vital Signs	X	X	X	X	X	X	X	X	
Weight +Height	X	X	X	X	X	X	X	X	
Symptom Driven Physical Exam[3]	X	X	X	X	X	X	X	X	
Adverse Events[4]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Collection of device events/malfunctions	X	X	X	X	X	X	X		
Laboratory Assessments									
Hematology	X	X	X	X	X	X	X	X	

Procedure	**Part B - Optional Treatment Extension - Days 86-365 (Weeks 13-52) [All participants]**								
	Treatment Period							**Follow-Up Period**	
Study Day	**Day 113 ±7 days**	**Day 141 ±7 days**	**Day 169 ±7 days**	**Day 211 ±7 days**	**Day 253 ±7days**	**Day 309 ±7days**	**Day 365 ±7 days**	**8-Week Follow-up ±7 days[1]**	**16-Week Follow-up ±7days [1,2]**
Study Week	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 30**	**Wk 36**	**Wk 44**	**Wk 52/EW[1]**	**Wk 60**	**Wk 68[2]**
Urinalysis	X	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	X	X	
Spot Urine (protein to creatinine ratio)	X	X	X	X	X	X	X	X	
Pregnancy Test[5]	X	X	X	X	X	X	X	X	X
C3/C4, CRP[10]			X				X	X	
B-Cells[10]			X				X	X	
Anti-dsDNA and ANA[10]			X				X	X	
Immunogenicity			X				X	X	
IgA, IgG and IgM[10]	X	X	X	X	X	X	X	X	
Belimumab Administration and PK Sampling									
Cohort 1 Administration of Belimumab (Body weight ≥50 kg)[6,9]	**Once weekly (±2 days) until Week 51 (inclusive)**								

Procedure	**Part B - Optional Treatment Extension - Days 86-365 (Weeks 13-52) [All participants]**								
	Treatment Period							**Follow-Up Period**	
Study Day	**Day 113 ±7 days**	**Day 141 ±7 days**	**Day 169 ±7 days**	**Day 211 ±7 days**	**Day 253 ±7days**	**Day 309 ±7days**	**Day 365 ±7 days**	**8-Week Follow-up ±7 days[1]**	**16-Week Follow-up ±7days [1,2]**
Study Week	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 30**	**Wk 36**	**Wk 44**	**Wk 52/EW[1]**	**Wk 60**	**Wk 68[2]**
Cohort 2 Administration of Belimumab (Body weight ≥30 kg to <50kg)[7,9]	**Every 10 days(± 2 days) until Day 361 (inclusive)**								
Cohort 3 Administration of Belimumab (Body weight <30kg)[8,9]	**Every 2 weeks (±2 days) until Week 50 (inclusive)**								
PK Sampling[10]	X		X		X		X	X	

1. If participants withdraw from treatment prior to Week 52, in addition to the 8- and 16-week follow-up visit and assessments, an early withdrawal (EW) visit should, if possible, be completed. The EW visit requires identical assessments and procedures to the Week 52 visit. The 8- and 16-week follow-up visits are **NOT** required for participants who are eligible for and are enrolled into the optional access extension phase.
2. 16-week follow-up requires a phone call to collect AEs, concomitant medications and report results of home urine pregnancy test (if applicable) for female participants. NOTE – the 16-week follow-up may be performed at a clinic visit per local requirement.
3. An abbreviated/symptom-driven exam can be done as described in Section 8.8.1
4. Please refer to Section 8.9.1 for the time period for collection of AEs/SAEs.
5. Urine pregnancy test is sufficient for all visits in Part B. A home pregnancy test (urine) will be provided to participants for the 16-week follow-up pregnancy assessment.
6. Cohort 1 (≥50 kg at baseline): Study drug to be administered weekly. Wherever the dosing days coincide with clinic visits IP administration in clinic is mandated. PK and/or biomarker sample collection, where specified, must be pre-dose at these visits.
7. Cohort 2 (≥30 kg - <50 kg at baseline): Study drug to be administered every 10 days. Wherever the dosing days coincide with clinic vists IP administration in clinic is mandated. PK and/or biomarker sample collection, where specified, must be pre-dose at these visits.
8. Cohort 3 (15 - <30 kg at baseline): Study drug to be administered every 2 weeks. Wherever the dosing days coincide with clinic visits IP administration in clinic is mandated. PK and/or sample collection, where specified, must be pre-dose at these visits.

9. In Part B the dosing frequency may be switched according to any change in body weight. Please refer to Section 6.6 Dose Modification. IF a participant switches dosing frequency due to weight changes during Part B, the last IP administration will be according to the schedule provided at Week44. Individual cases will be consulted with and resolved by the Medical Monitor.
10. Samples must be taken pre-dose where the dose is administered on a clinic visit day.

1.3.4. SOA 4 Optional Access Extension Phase - Applies exclusively to eligible participants who complete Part B

Note: Participants may need to switch dosing frequency according to changes in body weight (See Section 6.6 Dose Modification)

Procedure	Optional Access Extension phase - From Week52 [Eligible participants only]				
	Treatment Period			Follow-Up Period[1,2]	
Study Day	**Day 365 ±7 days**	**Visit Every 12 Weeks until the end of Access Extension ±7 days[1]**	**End of access extension /EW[1]**	**8-Week Follow-up ±7 days[1,2]**	**16-Week Follow-up ±7 days[1,2]**
Study Week	**Wk 52**				
Access Extension Phase Specific Eligibility Criteria	X				
Access Extension Phase -Specific Written Informed Consent	X				
Weight[3]	X	X			
Serious Adverse Events[4]	X	X	X	X	X
Collection of device events/malfunctions	X	X	X		
Laboratory Assessments					
Pregnancy Test[5]	X	X	X	X	X
Belimumab Administration					
Administration of Belimumab (Body weight ≥50 kg)[6,9]	X	X			
Administration of Belimumab (Body weight ≥30 kg to <50kg)[7,9]	X	X			

Procedure	Optional Access Extension phase - From Week52 [Eligible participants only]				
	Treatment Period			Follow-Up Period[1,2]	
Study Day	**Day 365 ±7 days**	**Visit Every 12 Weeks until the end of Access Extension ±7 days[1]**	**End of access extension /EW[1]**	**8-Week Follow-up ±7 days[1,2]**	**16-Week Follow-up ±7 days[1,2]**
Study Week	**Wk 52**				
Administration of Belimumab (Body weight <30kg)[8,9]	X	X			

1. If participants withdraw from treatment at anytime during the optional access extension phase, in addition to the 8- and 16-week follow-up visits, an early withdrawal (EW) visit should, if possible, be completed.
2. 8 and 16-week follow-up requires a phone call to collect SAEs, and the results of home urine pregnancy test (if applicable) for female participants. NOTE: the 8-Week and 16-week follow-up may be performed at a clinic visit per local requirement.
3. Any changes in body weight that lead to a change in dosing frequency should be noted and requested in the IWRS system as per Section 6.7.1.5(see SRM for details).
4. Please refer to Section 6.7.1.5for SAE reporting in the optional access extension phase and Section 8.9.1.for the time period for collection of SAEs.
5. For females of childbearing potential: urine pregnancy tests will be provided by sites. Participants will be required to perform a urine pregnancy test every 4 weeks throughout the treatment period (1 onsite and 2 at home). Home urine pregnancy tests will also be provided for the 8-week and 16-week follow-up period. The results of urine pregnancy tests conducted at home will be recorded in the subject diary cards and stored as part of the investigator's source documents. Only positive pregnancy test results will be reported to GSK during the optional access extension phase and will follow the guidance in Section 8.9.5.
6. Participants ≥50 kg at the start of the access extension phase: Study drug to be administered weekly. At home self-administration is encouraged.
7. Participants ≥30 kg - <50 kg at the start of the access extension phase: Study drug to be administered every 10 days. At home self-administration is encouraged.
8. Participants <30 kg at start of the access extension phase: Study drug to be administered every 2 weeks. At home self-administration is encouraged.
9. In the optional access extension phase the dosing frequency may be switched according to any change in body weight. Please refer to Section 6.6 Dose Modification.

2. INTRODUCTION

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 and SC formulations) is approved for the treatment of adult patients with active autoantibody positive systemic lupus erythematosus (SLE), a chronic autoimmune disorder characterized by autoantibody production and abnormal B lymphocyte function.

Three pivotal trials have been conducted to support the approval of belimumab for the treatment of adult participants SLE, including two Phase 3 trials using intravenous (IV) belimumab [Furie, 2011; Navarra, 2011] and one Phase 3 trial using the subcutaneous (SC) formulation [Stohl, 2017]. In these studies, belimumab treatment led to significant improvements in the SLE Responder Index (SRI) [Furie, 2009]. Pooled analyses demonstrated steroid sparing and decreased risk of severe flares over 52 weeks. Data from completed clinical studies are provided in the current Investigator Brochure (IB) and IB supplement(s) (if applicable). Clinical trial data for belimumab since its approval continue to show efficacy in the treatment of SLE through decreased SLE flares and decreased disease activity across multiple organ systems.

A multi-center randomized double-blind placebo-controlled clinical trial of IV belimumab in pediatric participants (BEL114055) is currently being conducted (see Section 2.2.1) in order to fulfill post-approval commitments to the FDA and EMA. Data generated from the current open-label study using the SC formulation in pediatric participants ages 5-17 years will be used to support extrapolation of safety and PK from the IV pediatric and SC adult randomized trials, in order to support an alternative mode of administration of belimumab to pediatric SLE patients.

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

2.1. Study Rationale

BENLYSTA for SC use is licensed in over 30 countries for the treatment of adult patients with active, autoantibody-positive SLE who are receiving standard of care therapy. The approved dose is 200 mg weekly SC and is available in a prefilled syringe and an autoinjector device. The purpose of this study is to evaluate the pharmacokinetics (PK), safety, and pharmacodynamics (PD) of repeat doses of 200 mg belimumab administered subcutaneously (SC) in pediatric participants 5 to 17 years of age with SLE on a background of standard of care therapy. This bridging PK study is part of an extrapolation strategy to support the use of SC belimumab in pediatric SLE patients, based on the completed adult SLE study with SC belimumab and the pediatric SLE study with IV belimumab, and is a component of a post-approval commitment to EMA (EMA-000520-PIP02-13-M01) and FDA (PMR 3239-1, BLA 761043**).** Availability of SC belimumab could potentially benefit the pediatric SLE population by allowing at-home administration and reducing the burden of IV infusions and time spent at the doctor's office/infusion center.

2.2. Background

Like other rheumatic diseases of childhood, childhood-onset SLE (cSLE) is not identical to adult-onset SLE [Lehman, 2007]. Compared with adult SLE, cSLE patients have more active disease both at the time of diagnosis and over time. cSLE is associated with more rapid accrual of organ damage, and a higher degree of morbidity compared with adult onset SLE [Brunner, 2008; Tucker, 2008]. Several studies suggest that glomerulonephritis is more prevalent in cSLE compared to adult-onset SLE [King, 1977; Barron, 1993; Fish, 1977]. In addition, cSLE has a significantly higher occurrence of neurological involvement at the time of diagnosis [Tucker, 2008]. Development of safe and effective treatments for cSLE therefore remains an area of high unmet need.

2.2.1. Study of IV Belimumab in Pediatric SLE Study Participants

BEL114055 is the first randomized placebo-controlled trial to test for treatment effect on disease activity outcomes in pediatric SLE. BEL114055 is a three-part study. In Part A (52-week double-blind treatment phase), participants were randomized to receive IV belimumab or placebo in addition to standard of care SLE therapy. Participants who completed Week 52 of Part A were eligible to participate in Part B, a 10-year open-label continuation phase. Participants discontinuing study agent in Part A or Part B were eligible for enrollment into Part C, the long-term safety follow-up phase. Parts B and C are ongoing. Part A was completed in January 2018. Due to the rarity of SLE in children and the resulting recruitment challenges, BEL114055 was not powered by design, and therefore no hypothesis testing was performed. Of the 93 participants enrolled in BEL114055, 40 participants were randomized to placebo and 53 participants to IV belimumab in Part A. Thirteen participants were 5 to 11 years of age and 80 participants were 12 to 17 years of age at the time of screening. Within the limits of the 1-year data analyzed to date, the risk/benefit profile of IV belimumab 10 mg/kg in pediatric SLE patients appears consistent with that of the adult patient population.

2.2.1.1. Efficacy of IV Belimumab in Pediatric SLE Study Participants

Similar to the pivotal adult IV [Furie, 2011; Navarra, 2011] and SC [Stohl, 2017] studies, the primary endpoint for Part A of BEL114055 was the SRI at Week 52. A major secondary endpoint was the Week 52 PRINTO/ACR Juvenile SLE Response Evaluation (PRINTO), a novel pediatric-specific composite endpoint used for the first time in a placebo-controlled clinical trial. The PRINTO tool assessed percent improvement from baseline to Week 52 in the following five domains: 1) SELENA SLEDAI, 2) Physician's Global Assessment, 3) Parent's Global Assessment, 4) 24-hour proteinuria, and 5) Pediatric Quality of Life physical functioning. Other major secondary endpoints included the individual PRINTO components, the proportion of participants with a sustained SRI response, and the proportion of participants with a sustained parent global assessment (parent GA) response. Risk of lupus flares was also assessed.

From the double-blind (Part A) phase of BEL114055, the following results have been reported [Brunner, 2018]:

- A numerical benefit of belimumab 10 mg/kg was shown over placebo for the primary efficacy endpoint of SRI response rate at Week 52. The treatment difference (belimumab vs. placebo) at Week 52 was consistent with those observed in adult IV belimumab studies and the results for SRI6 and sustained SRI response also favored belimumab.
- The key secondary PRINTO/ACR endpoints indicated a greater benefit of belimumab with 4 of the 5 individual components (percent change in ParentGA, PGA, SELENA SLEDAI, and proteinuria) showing a numerical benefit of belimumab compared with placebo.
- A higher percentage of belimumab participants had a sustained ParentGA response at Weeks 44-52 vs. placebo.
- Participants in the belimumab group had a lower risk of experiencing a severe SFI flare compared with the placebo group.
- More than 50% of pediatric participants exceeded the MCID for improvement in the PedsQL generic total score, with no difference between the belimumab and placebo groups.

2.2.1.2. Pharmacokinetics of IV Belimumab in Pediatric SLE Study Participants

Following IV administration of 10 mg/kg on Days 0, 14, and 28 and every 4 weeks thereafter, the approved adult SLE dosing regimen, belimumab exposures were similar between pediatric and adult SLE participants [GSK document number 2017N34326_00]. Steady-state geometric mean Cmax, Cmin, Cavg, and AUC values were, respectively, 315, 50, 108 µg/mL, and 3012 day µg/mL in the overall pediatric population; 305, 42, 92 µg/mL, and 2569 day µg/mL in the 5-11-year-old group, and 317, 52, 112 µg/mL, and 3126 day µg/mL in the 12-17-year-old group compared to 311, 46, 100 µg/mL, and 2811 day µg/mL in adults. The slightly decreased exposure in younger participants was expected due to their lower BMI and allometric principles.

2.2.1.3. Pharmacodynamics of IV Belimumab in Pediatric SLE Study Participants

Similar to results of adult IV [Stohl, 2012] and SC [Doria, 2018] studies, reductions in overall B cells, naive B cells, other B cell subsets, and immunoglobulins were observed following IV belimumab administration in pediatric participants in Part A of BEL114055 [GSK document number 2017N34326_00].

2.2.1.4. Safety of IV Belimumab in Pediatric SLE Study Participants

In the double blind phase (Part A) of BEL114055, treatment with IV belimumab plus standard of care was generally well-tolerated. Overall, no new safety concerns were identified during Part A, relative to the known safety profile of IV and SC belimumab in adult SLE clinical trials as described in the current IB and IB supplement(s) (if applicable).

The proportion of participants withdrawn from Part A due to an adverse event was 12.5% of placebo participants compared with 5.7% of belimumab participants. Serious adverse events were reported in 35.0% of placebo participants compared with 17.0% of belimumab participants, and only lupus nephritis led to discontinuation in more than 1 participant (2 [5%] placebo, 1 [1.9%] belimumab).

The most common AE reported in both treatment groups during the study was headache (27.5% placebo, 13.2% belimumab). AEs reported in >5% of belimumab-treated participants and at an incidence at least 3% greater than that observed with placebo were diarrhea, rash, neutropenia, and increased transaminases.

The system organ class (SOC) with the highest incidence in both treatment groups was infections and infestations for AEs (70.0% placebo, 56.6% belimumab) and SAEs (12.5% placebo, 7.5% belimumab). Opportunistic infections, including active tuberculosis and herpes zoster, were not reported in the placebo group and one (1.9%) participant in the belimumab group had an opportunistic herpes zoster infection. There were no malignancies reported. During Part A, there were no deaths in the belimumab group and one subject in the placebo group died of acute pancreatitis.

2.3. Benefit/Risk Assessment

Overall, the positive benefit/risk profile of IV belimumab in the BEL114055 pediatric SLE cohort appears consistent with that of adult IV and SC study populations. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of belimumab may be found in the current 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 PML. Fatal infections have been reported in SLE patients receiving immunosuppressant therapy, including belimumab.	The rate of serious infections for SLE is ~5% of participants receiving either belimumab or placebo.	Exclusions (see Section 5.1) 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 HIV infection, and grade 3 (or greater) hypo gammaglobulinemia or (if unrelated to SLE) grade 3 (or greater) neutropenia, lymphopenia, leukopenia will be applied. Participants whose IgG level falls below 250 mg/dL will have belimumab treatment withheld (See Section 8.8.4 Clinical Laboratory Assessments), and the appropriateness to continue dosing must be discussed and agreed with the Medical Monitor before the next dose. Any participant whose IgG level falls below 250 mg/dL and is associated with a severe or serious infection will have study agent permanently discontinued. A diagnosis of PML should be considered in any participant presenting with new-onset or deteriorating neurological signs and symptoms. The participant should be referred to a

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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 in Part A. The presence of ADAs will be monitored with collection at baseline, Weeks 4, 12, 24, 52, and 8-week post-treatment follow-up. Participants will be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Patients 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 patients for signs and symptoms of malignancy, monitor laboratory values, request that patients report signs and symptoms. Treat appropriately.
Interactions with Vaccinations		
Because of its mechanism of action, belimumab may interfere with the response to immunizations.	The efficacy of concurrent vaccination in patients receiving belimumab is not known; however, in the belimumab vaccination trial, evaluation of the impact of belimumab treatment on response to on-treatment vaccination with 23-valent pneumococcal vaccine revealed that immune responses to the different serotypes were similar in SLE patients receiving belimumab compared with those not receiving treatment at the time of vaccination.	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 subjects with SLE (1:1 randomization): Serious adverse events (SAE)	Participants who, in the investigator's opinion, pose a significant suicide risk will be excluded. Monitor participants for psychiatric signs and symptoms, request that patients report

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	of suicidal ideation or behavior or self-injury were reported in 0.7% (n= 15) of subjects receiving belimumab intravenously 10 mg/kg (IV) vs. 0.2% (n=5) of subjects taking placebo. No suicide-related deaths were reported. SAEs of depression were reported in 0.3% (n=7) of subjects receiving belimumab 10 mg/kg IV vs. <0.1% (n=1) taking placebo. On the Columbia-Suicide Severity Rating Scale (C-SSRS), 2.4% (n=48) subjects on belimumab 10 mg/kg IV reported suicidal ideation or behavior and 2.0% (n=39) subjects 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 ISO 14971, "Application of Risk Management to Medical Devices." Accordingly, all potential risks posed by the user during operation of device for self-	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
	administration have been identified and evaluated. 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 SLE Responder Index and time to first severe flare endpoints. Overall efficacy of IV belimumab in a randomized placebo-controlled clinical trial in pediatric patients with SLE (BEL114055) was consistent with that seen in adult patients (see Section 2.2.1.1).

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures that will be implemented to minimize risk to patients 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 patients with SLE who choose to participate in this trial.

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary - Pharmacokinetics	
• To characterize the PK profile of belimumab 200 mg SC in pediatric SLE participants.	• Observed belimumab concentrations at Week 12. • Steady-state PK parameters: Cavg (AUC), Cmax, Cmin (based on population PK estimates).
Secondary - Safety	
• To evaluate the safety and tolerability of belimumab 200 mg SC in pediatric SLE participants.	• Incidence of adverse events, serious adverse events and adverse events of special interest through Week 52.
Secondary - Biomarkers	
• To characterize the pharmacodynamic profile of belimumab 200 mg SC in pediatric SLE participants.	• Change from baseline in biomarkers (C3/C4, anti-dsDNA, B cell subsets, and immunoglobulins) at Weeks 12 and 52.
Other - Efficacy	
• To characterize the impact of belimumab 200 mg SC on disease activity in pediatric SLE participants.	• Percent of subjects with a ≥ 4 point reduction from baseline in SELENA SLEDAI at Weeks 12 and 52.

4. STUDY DESIGN

4.1. Overall Design

Please refer also to the study Schema (Section 1.2).

This is a single arm, multi-center open-label study to evaluate the PK, safety, and PD of SC belimumab plus background standard therapy in approximately 28 pediatric participants 5 to 17 years of age and weighing ≥15 kg with active SLE. The study will include:

- Part A: Open-label, 12-week treatment phase
- Part B: Optional 40 week open-label continuation phase for any participant who completes Part A
- Post-treatment follow-up assessments at 8 and 16 weeks after the last dose of SC belimumab
- Optional Access extension Phase: Optional post-Week 52 extension phase exclusively for eligible participants who complete Part B (e.g., participants from countries where the IV formulation is not approved for pediatric use; or

participants in whom IV Benlysta is not suitable due to medical reasons or significant logistical challenges;see Section 6.7.1).

Part A is an open label 12-week treatment phase to evaluate the PK, safety, and PD of 200 mg belimumab administered SC via autoinjector in pediatric participants with active SLE (SLE diagnosis confirmed by revised ACR criteria and SELENA SLEDAI score ≥6 at screening, with at least 12 participants with a SELENA SLEDAI score of ≥8 at screening). Approximately 28 participants will be enrolled and allocated to treatment cohorts based on their body weight at baseline. The total enrolment is aimed to ensure that approximately 24 participants are evaluable at Week 12 to have sufficient data to accurately characterize the PK in this pediatric population. Enrollment and study withdrawals will be closely monitored and if there is an impact on continuation of participants in the study due to the Coronavirus SARS-CoV-2 (COVID-19) pandemic, more than 36 participants may be screened and more than 28 may need to be enrolled, to ensure the ability to achieve the evaluable target at Week 12.

Administration of belimumab 200 mg SC in Part A will be as follows:

Cohort	Body weight at baseline (kg)	Dosing frequency
1	≥50	Every week (QW)
2	≥30 to <50	Every 10 days (Q10d)
3	<30	Every 2 weeks (Q2W)

Cohort 1, Cohort 2, and Cohort 3 will be recruited in parallel.

Belimumab will be administered in addition to standard of care therapy for SLE. Participants and/or caregivers will be trained to use the autoinjector to administer the study agent. The first three doses will be administered under observation in the clinic and the first two doses must also be followed by 3 hours post dose clinical observation (see Section 6.4). Subsequent doses may be administered away from the clinic except where in clinic dosing is specified in the SoA (Section 1.3).

Blood samples for PK, PD, and safety monitoring will be obtained as indicated in the SoA (Section 1.3). For participants not continuing to Part B, an 8-week follow-up visit will take place and in addition, AEs, concomitant medications and the results of a home urine pregnancy test will be collected by phone (or at the clinic as per local requirement) at the 16-week post treatment follow-up assessment.

Part B is an optional 40-week open-label continuation phase, open to all participants who have completed Part A. Dosing of SC belimumab may continue at the same frequency in Part B or may require a change in frequency according to changes in participant body weight (see Section 6.6 for details). Participants will return to the clinic for safety

assessments at regular intervals as defined in the SoA (Section 1.3). Samples for PK analysis and for immunogenicity and biomarkers will be obtained as indicated in the SoA (Section 1.3). AEs, concomitant medications and the results of a home urine pregnancy test will be collected by phone (or at the clinic as per local requirement) at the 16-week post-treatment follow-up.

The study Medical Monitor and members of the GSK Safety Review Team (SRT) (Section 9.4.1) will perform in-stream review of all safety data throughout Part A and Part B of the study.

In parallel, a GSK PK Review Team (PRT) (Section 9.4.2) will review all available PK data after the first 6 participants in Cohorts 1 (≥50 kg) or 2 (≥30 kg to <50kg) have completed Week 12. For Cohort 3 (<30 kg), preliminary PK data will be reviewed by the PRT based on a data cut triggered by the first Cohort 3 participant having completed Week 12. The primary objective of the PRT meetings will be to either confirm the initial dose or to recommend any adjustments.

Participants may withdraw or discontinue from the study at any time for any reason (see Section 7.2).

The total maximum duration of study participation for each participant is 73 weeks (screening:5 weeks, treatment: up to 52 weeks [12 weeks Part A plus 40 weeks extension phase] and follow-up: 16 weeks) unless they are included in the optional access extension phase.

Optional Access Extension Phase is an optional extension phase to provide a mechanism for continued access to belimumab SC from Week 52 and is exclusive only for eligible participants who complete Part B of the study. The conditions of eligibility into the optional access extension phase will be reviewed against the access extension specific eligibility criteria, detailed in Section 6.7.1. The duration of this phase is dependent upon participants' ages and the conditions of eligibility to the optional access extension phase. Participants who are enrolled into the optional access extension phase will be withdrawn from treatment if they reach the age of 18 years, if Belimumab SC or IV becomes licensed and commercially available for pediatric use in the participant's country (see Section 6.7.1.4for full withdrawal criteria).

In the optional access extension phase, after Week 52 visit, participants will return to the clinic every 12 weeks to receive their autoinjectors for at home administration and safety assessments, as defined in the SoA (Section 1.3). Dosing of SC belimumab may continue at the same frequency or may require a change in frequency according to changes in participant body weight (see Section 6.6 for details). At 8 and 16-week follow-up visits, SAEs and the results of home urine pregnancy tests will be collected by phone (if applicable). The 8-Week and 16-week follow-up may be performed at a clinic visit per local requirement.

4.2. Scientific Rationale for Study Design

The results from study BEL114055 (Section 2.2.1) are consistent with a positive risk benefit of IV belimumab 10 mg/kg for the treatment of SLE in pediatric population from

5 to 17 years of age and are consistent also with the positive risk benefit of belimumab IV and SC formulations in the adult population. This study aims to confirm that belimumab SC formulation in the pediatric study population has consistent PK and safety profile with belimumab in adult population, and with IV belimumab in pediatric population.

The study is to support the use of belimumab SC in the pediatric population, thereby providing treatment options and allowing patients the potential to administer their medication at home, and decreasing the burden of visits to an infusion center.

The 12-week open-label PK, safety, and PD study of SC belimumab will be followed by an optional open-label 40-week continuation phase. The open-label trial design, in combination with a partial PK extrapolation strategy, is expected to provide longer term data on belimumab SC formulation in this trial population.

4.3. Justification for Dose

The dose and dosing regimens selected for SC administration in this pediatric population are intended to achieve a similar average exposure as observed with the weekly 200 mg SC dosing regimen in adult SLE patients, estimated at 104 µg/mL from a population PK analysis of SC study data in adults [GSK Document Number 2015N263802_01].
For a fixed belimumab dose the exposure increases as body weight decreases, as observed in adults and supported by the population PK model developed from the pediatric IV study BEL114055. To accommodate children between the ages of 5 to 17, specifically to ensure lower body weight subjects are not over-exposed, three belimumab SC dose groups are proposed and defined by body weight. Pediatric subjects weighing 50 kg or more will receive 200 mg belimumab once a week (QW), as per the recommended dosing regimen in adults. Pediatric participants who weigh between 30 to 50 kg will receive as 200 mg belimumab administered once every ten days (Q10d). Pediatric participants weighing less than 30 kg will receive 200 mg belimumab once every two weeks (Q2W).

The proposed 30 and 50 kg weight thresholds approximately correspond to the age groups 5-9 years, 9-14 years, and 14 years or older - according to the CDC growth chart 9.3 and 14.2-year-old girls have median weights of 30.1 and 50.0 kg, respectively. [https://www.cdc.gov/growthcharts/clinical_charts.htm#Set1].

The pediatric population PK model for IV administration, developed from the pediatric IV study data (BEL114055 CSR), was extended to include SC dosing by incorporating the absorption components of the adult SC PK model [GSK Document Number 2015N263802_01]. The resulting model was used to simulate the three dose groups for 200 mg SC: (1) Q2W for <30 kg; (2) Q10d for ≥30 kg and <50 kg; (3) QW for ≥50 kg subjects. The simulations sampled a pediatric population biased towards females (90%) which is typical of an SLE population. Body size parameters (body weight and BMI) were sampled from the NHANES 2015-2016 database and restricted to pediatric subjects between the ages of 5 and 18 years. Other covariates which form model input parameters were sampled from the pediatric study BEL114055 dataset.

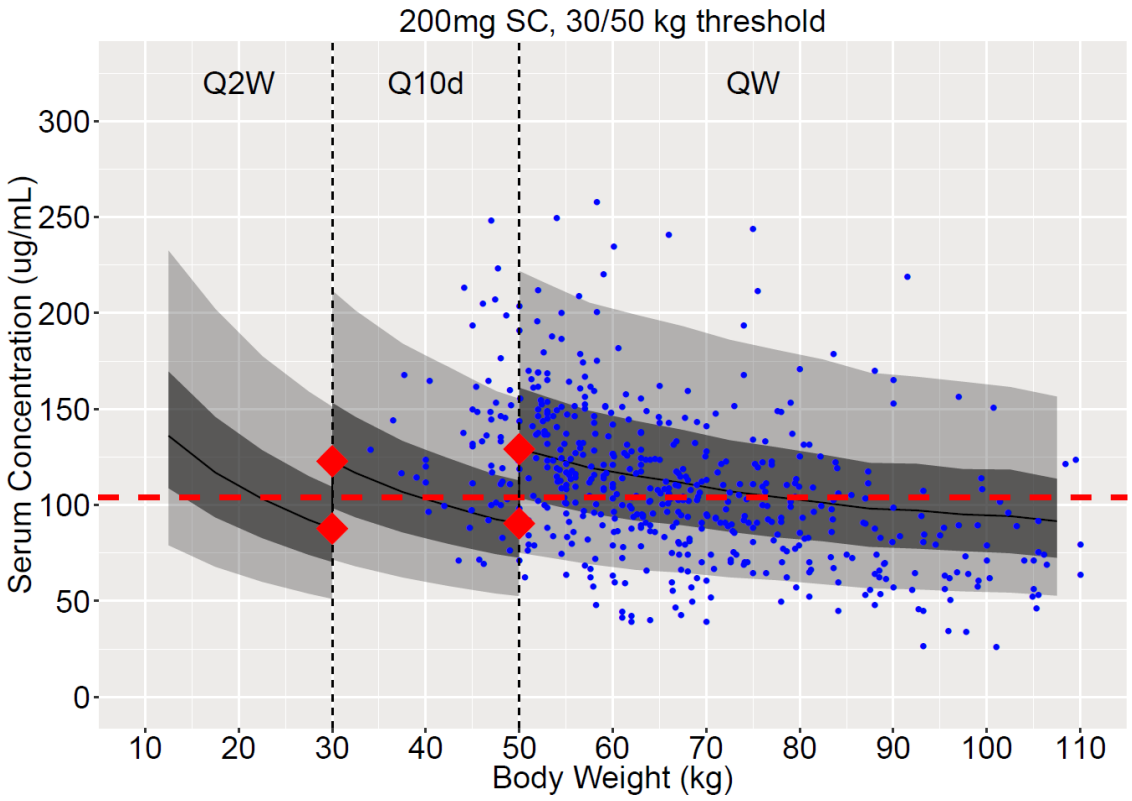
For the proposed dosing regimen, the range of exposures in the three dose groups (Q2W <30kg, Q10d ≥30 to <50kg, QW ≥50kg) are very similar (Figure 1, Table 1). At the 30

kg threshold exposure is predicted to be ~15% below and above the target concentration, namely 88 µg/mL (Q2W) and 123 µg/mL (Q10d) relative to the 104 µg/mL target. Similarly, at the 50 kg threshold subjects receiving belimumab Q10d also have exposures 15% below the target value (90 µg/mL vs 104 µg/mL target). For 50 kg subjects receiving QW dosing the exposure is a little higher, predicted to be ~25% above the target (129 µg/mL vs 104 µg/mL target). However, this specific value represents the largest deviation from the target along the exposure-weight relationship for body weights >15 kg (the cut-off weight for enrolment) and does not constitute an "over-exposure" considering the much larger between-subject variability not explained by body weight. In addition, several adults weighed less than 50 kg, similar to pediatrics, and were not considered to have unjustifiably large exposures even though the adults received 200 mg QW.

The exposures across the three dose groups are generally centred about the target value (104 µg/mL), with almost identical between subject variability at steady state (Figure 2). Additionally, the variability in the average exposure in any of the three dose groups, as expressed by the 90% prediction interval (light grey region, Figure 1), does not fall outside the range of exposures observed in adults (blue points, Figure 1). As a result, since no exposure-response relationship for safety was apparent in the adult SC population analysis, or in the pediatric IV study BEL114055, no safety concerns are expected in any of the three dose groups based on the PK predicted for pediatrics.

In summary, belimumab PK in pediatrics is predicted to be very similar across the three dose groups. Within each group, steady state concentrations are centred on the target value (104 µg/mL), between-subject variability is consistent with observed adult data, and deviations from the target exposure are within acceptable limits (≤25% at the body weight thresholds). Therefore, the three-tier dosing regimen, with Q2W dosing for subjects <30 kg, Q10d dosing for subjects between 30 and <50 kg, and QW dosing for subjects ≥50 kg is considered appropriate for study 200908.

Figure 1 Average serum concentrations at steady state versus body weight.



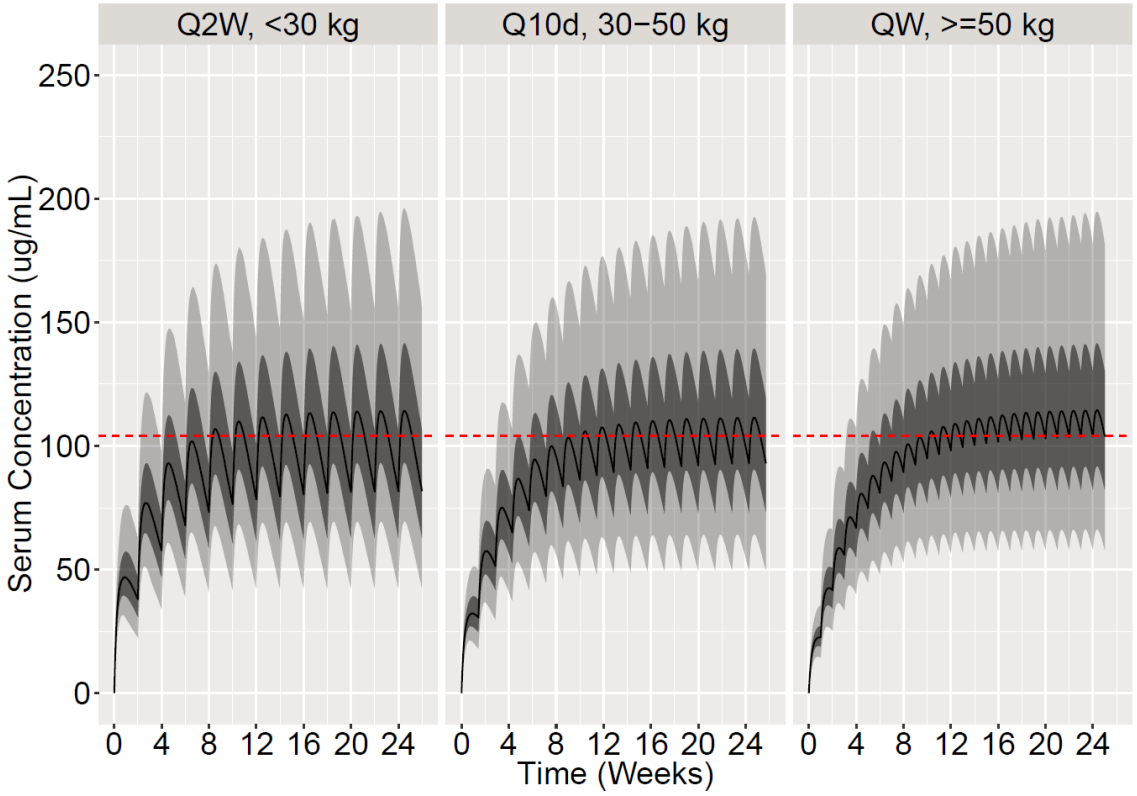
Pediatric predictions for the median (solid black line), inter-quartile range (dark grey shaded region) and 90% prediction interval (light grey shaded area) are compared with the post-hoc adult estimates (blue points) and the population adult estimate (broken red, 104 μg/mL). The median pediatric concentrations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

Table 1 Average serum concentrations at steady state as a function of body weight.

Regimen	Dose	Body Weight (kg)	Serum Concentration (μg/mL)
30/50 kg body weight threshold[a]	Q2W <30kg	30	88
	Q10d 30-50 kg	30	123
		50	90
	QW ≥50 kg	50	129
Adults	QW	67	104[b]

a. 1-week dosing period switches to 1 dose every 10-days at 50 kg and then to 1 dose every 2-weeks at 30 kg.
b. Estimate based on population parameters from the adult population PK model for SC belimumab administration.

Figure 2 Time course profiles for the three dose groups defined by 30 kg and 50 kg weight thresholds.



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 population adult estimate (broken red, 104 μg/mL).

4.4. End of Study Definition

A participant is considered to have completed the primary study if he/she has completed Part A and Part B of the study up to and including the Week 52 visit. Participants who elect not to join the optional Part B will be considered to have completed Part A of the study if all visits up to Week 11/12 (Day 81-85) are completed. Eligible participants who complete Part B may be enrolled into the optional access extension phase of the study from Week 52 (Section 6.7.1).

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 optional access extension phase.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participant must be between 5 and 17 years of age inclusive, at the time of Day 1.

Type of Participant and Disease Characteristics

2. Participants who meet the 1997 American College of Rheumatology (ACR) criteria for the classification of SLE (Appendix 8)
    a. Have or have had in series 4 or more of the 11 ACR criteria for the classification of SLE
3. Have active SLE disease defined as a SELENA SLEDAI score ≥6 at screening (Appendix 9).
4. Have documented positive autoantibody test results within the study screening period, defined as an ANA titre ≥ 1:80 and/or a positive anti-dsDNA (≥30 IU/mL) serum antibody test based on EITHER the study's central laboratory results OR the local laboratory results. Only unequivocally positive values as defined in the laboratory's reference range are acceptable; borderline values will not be accepted.
5. Are on a stable SLE treatment regimen.

"Stable treatment at baseline" consists of any of the following medications (alone or in combination) administered for a period of at least 30 days prior to Day 1:

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

- For those participants on alternating day doses of steroids, use the average of 2 daily doses to calculate the average daily steroid dose.
- Other immunosuppressive or immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), calcineurin inhibitors (e.g. tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine or thalidomide.
- Anti-malarials (e.g. hydroxychloroquine, chloroquine, quinacrine)
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- New SLE therapy must not be added within 30 days of Day 1.

Weight

6. Body weight ≥15 kg.

Sex

7. Male and/or female

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

Male Participants

No contraceptive measures are required for male participants.

Female participants:

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

- Is not a woman of childbearing potential (WOCBP) (See Appendix 4)

OR

- Is a WOCBP and is using a contraceptive method that is highly effective, with a failure rate of <1%, as described in 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

8. 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 Parts A and B of the study if any of the following criteria apply:

Medical Conditions

1. Have an estimated glomerular filtration rate (eGFR) as calculated by Schwartz Formula [Schwartz, 2009] of less than 30 mL/min.
2. Have acute severe nephritis defined as significant renal disease (e.g., the presence of urinary sediments and other lab abnormalities) that, in the opinion of the study investigator, may lead to the participant requiring induction therapy during the first 12 weeks of the trial.

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

3. Have a history of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoetic stem cell/marrow transplant.
4. Have clinical evidence of significant, unstable or uncontrolled, acute or chronic diseases not due to SLE (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy or infectious diseases) which, in the opinion of the investigator, could confound the results of the study or put the participant at undue risk.
5. Have a planned surgical procedure or a history of any other medical disease (e.g., cardiopulmonary), laboratory abnormality, or condition (e.g., poor venous access) that, in the opinion of the investigator, makes the participant unsuitable for the study.
6. Have a history of malignant neoplasm within the last 5 years.
7. Have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months, or who in the investigator's opinion, pose a significant suicide risk.
8. Have a history of a primary immunodeficiency.

9. Have an IgA deficiency (IgA level <10 mg/dL).

10. Have acute or chronic infections requiring management, as follows:
    - Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
    - Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) for infection within 60 days of Day 1.

11. Have a Grade 3 or greater laboratory abnormality based on the protocol defined Adverse Event and Laboratory Value Severity Grade scale (Appendix 2, Section 10.2.1) except for the following that are allowed:
    - Stable Grade 3 prothrombin time (PT) secondary to warfarin treatment.
    - Stable Grade 3 partial thromboplastin time (PTT) due to lupus anticoagulant and not related to liver disease or anti-coagulant therapy.
    - Stable Grade 3 hypoalbuminemia due to lupus nephritis, and not related to liver disease or malnutrition.
    - Any grade proteinuria.
    - Stable Grade 3 gamma glutamyl transferase (GGT) elevation due to lupus hepatitis, and not related to alcoholic liver disease, uncontrolled diabetes or viral hepatitis. If present, any abnormalities in the ALT and or AST must be ≤ Grade 2.
    - Stable Grade 3 neutropenia; or stable Grade 3 lymphopenia; or stable Grade 3 leukopenia, due to SLE.

12. Have 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.

Prior/Concomitant Therapy

13. Have ever received treatment with belimumab (BENLYSTA).

14. Have received any of the following within 364 days of Day 1:
    - Treatment with any B-cell targeted therapy (e.g., rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI-Fc)
    - Abatacept.
    - Any biologic investigational agent

15. Have required 3 or more courses of systemic corticosteroids for concomitant conditions (e.g., asthma, atopic dermatitis) within 90 days of Day 1 (topical or inhaled steroids are permitted).

16. Have received any of the following within 90 days of Day 1:

- Anti-TNF therapy (e.g., adalimumab, etanercept, infliximab).
- Interleukin-1 receptor antagonist (anakinra).
- Intravenous immunoglobulin (IVIG).
- Plasmapheresis.

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

Prior/Concurrent Clinical Study Experience

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

Diagnostic assessments

22. Positive immunodeficiency virus (HIV) antibody test.
23. Hepatitis B: Serologic evidence of Hepatitis B (HB) infection defined as Hepatitis B surface antigen positive (HBsAg+) OR Hepatitis B core antibody positive (HBcAb+).
24. Hepatitis C: Positive test for Hepatitis C antibody confirmed on an additional blood sample by RNA PCR assay. Participants who are positive for Hepatitis C antibody and negative when the Hepatitis C RNA-PCR assay is performed on an additional sample will be eligible to participate. Participants who are positive for Hepatitis C antibody and have a positive result for the HCV when the Hepatitis C RNA PCR assay is performed on the additional sample will not be eligible to participate. (Institution or country specific guidelines for blood sample volume limits must be followed in collection of the additional blood sample.)

Other Exclusions

25. Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 364 days prior to Day 1.
26. 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.
27. Children in Care: A Child in Care (CiC) is a child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a CiC can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The determination of whether a child meets the definition of CiC should be made with the study centre staff in consultation with the responsible IRB/Ethics Committee.

5.3. Lifestyle Considerations

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

5.4. Screen Failures and Rescreening

Screen failures are defined as participants who consent to participate in the clinical study but following the screening assessments are not subsequently enrolled 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, and any serious adverse events (SAEs).

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

5.5. Repeat Assessments during the 35 Day Screening Period

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

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

6. STUDY INTERVENTION

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

6.1. Study Intervention Administered - Belimumab

ARM Name	Open label arm
Intervention Name	Belimumab
Type	Biologic
Dose Formulation	SC Injection
Unit Dose Strength(s)	200 mg/mL
Dosage Level(s)	Cohort 1 (≥50 kg): 200 mg weekly; Cohort 2 (≥30 kg - <50 kg): 200 mg every 10 days; Cohort 3 (<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 in cartons (1 autoinjector/carton). Each carton will be labeled as required per country requirement.
Manufacturer:	**Pre-filled syringe**: Pre-filled syringe components are procured from Becton Dickinson. Pre-filled syringe is filled with drug product and assembled at GSK, Barnard Castle, UK. **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: a pre-filled syringe contained within 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 (see Section 8.9.6).

6.1.1.1. Training for Use of Autoinjectors

Instructions for autoinjector use are provided in the Study Reference Manual. Training will also be provided to sites as described in the Study Reference Manual. Sites will provide training to participants and caregivers and will also provide them with an Instructions for Use. A link for online directions on how to use the autoinjector is provided for reference by site personnel so they are better able to instruct participants/caregivers on correct use.

6.2. Preparation/Handling/Storage/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 by the Interactive Web Response System (IWRS) 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.

- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study with a single treatment arm. The treatment (belimumab) to be taken by a participant will be centrally assigned using an IWRS. The site will contact the IWRS prior to the start of belimumab administration for each participant.

6.4. Subcutaneous Administration of Belimumab

"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.

During screening and on Day 1 (prior to the participant receiving their first dose), qualified study site personnel must review study drug handling and administration techniques with the participant and their caregiver(s). After the first injection of belimumab on Day 1, all subsequent injections should be administered according to the schedule shown in the SOA Section 1.3 ±2 days. Please refer to Section 6.4.2 for guidance regarding missed doses.

If possible, the participant or their caregiver will administer the study agent by SC injection even if administered at the clinic visit. The first three doses will be administered under observation in the clinic. In the post-marketing setting with IV belimumab, delayed onset of symptoms of acute hypersensitivity reactions have been observed. Therefore, at each of the first 2 scheduled administrations of belimumab, participants will be observed by qualified site staff during dosing and will remain under observation at the clinic for 3 hours post-dose. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgement. Participants and caregivers should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

Following the 3rd scheduled administration, where allowed by the schedule of activities (see Section 1.3 for definition of which scheduled belimumab injections must be done in clinic), at the discretion of the investigator, participants and caregivers who are adequately trained should administer subsequent doses of belimumab at home following the instructions provided. 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, although self-administration should be strongly encouraged. 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

6.4.1.1. Parts A and B

In Parts A and B, participants and caregivers will be provided with an injection diary (refer to SRM). Dosing compliance must be reviewed with the participant/caregiver at each site visit, the injection diary must be reviewed by study site staff and the entries transcribed to the 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, 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. 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 during Part A, then the Investigator must contact the Medical Monitor to discuss whether the participant should continue in the study (see SRM for details).

If a participant misses 3 or more consecutive doses of belimumab or 4 or more non-consecutive doses of belimumab during Part B, then the Investigator must contact the Medical Monitor to discuss whether the participant should continue in the study. If the participant is allowed to continue they must receive their next dose of belimumab in the

clinic and remain in the clinic for at least 3 hours for observation, as described in Section 6.4 for the initial 2 doses of belimumab.

6.4.2.1. Partial Doses

If a participant has administered a partial dose or was unable to completely self-administer a dose of belimumab due to malfunction of the autoinjector or user error, the participant/caregiver should be instructed to SKIP additional attempts and not re-inject for that period's belimumab dose. Thereafter, the participant should resume self-administering belimumab injections according to their next scheduled day of administration. The participant should not self-administer 2 doses on the same day, even if they believe that they did not receive any medication from the first administration attempt. (See Section 8.9.7– Medical Device Malfunctions).

6.5. 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.

6.5.1. Permitted Concomitant Therapy

Participants must be on a stable SLE treatment regimen for at least 30 days prior to Day 1. Corticosteroids may be added as new medications or their doses adjusted only up to 30 days prior to Day 1.

Once the participant has treatment assigned by the IWRS and receives the first dose of belimumab on Day 1, the investigator may adjust concurrent medications (add, eliminate, change dose level/frequency) as clinically required; however, changes in certain medications (as outlined below) may result in the participant being withdrawn from the study.

6.5.1.1. Anti-malarials

- A new anti-malarial (e.g., hydroxychloroquine, chloroquine, quinacrine) may be started between Day 1 and the 16-week follow-up assessment.
- The dose of an anti-malarial may be reduced or increased as clinically required, between Day 1 and the 16-week follow-up assessment.
- An anti-malarial may be replaced by another anti-malarial due to documented toxicity or lack of availability at any time during the study.

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.

6.5.1.2. Steroids

6.5.1.2.1. Systemic Steroids for SLE-related Disease Activity

- The total dose of systemic steroids may be increased or decreased as clinically indicated from Day 1 through the 16-week post-treatment follow-up assessment (see Section 1.3). Treatment of SLE Flares with Steroids: If a participant has an SLE flare requiring an increase in steroid dose the investigator should consider the guidelines prepared for the ACR, for steroid dose/duration of induction therapy [Ad Hoc Working Group on Steroid-Sparing Criteria in Lupus, 2004].

6.5.1.2.2. Intra-articular Injections of Corticosteroids

- Participants may receive intraarticular (IA) corticosteroid injections at any time between Day 1 and the 16-week follow-up assessment.

6.5.1.2.3. Steroids for Reasons Other Than SLE Disease Activity

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

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

6.5.1.3. Other Immunosuppressive/Immunomodulatory Agents

- Starting any new allowable immunosuppressive/immunomodulatory agent is permitted from Day 1 through the 16-week post-treatment follow-up assessment (See guidance in the SRM).
- The dose of existing immunosuppressive/immunomodulatory agents may be increased or decreased, as clinically required, from Day 1 through the 16-week post-treatment follow-up assessment.

An immunosuppressive/immunomodulatory agent may be replaced with 1 of the agents above due to documented toxicity or lack of availability. New topical immunosuppressive agents (e.g., eye drops, topical creams) are allowed from Day 1 through the 16-week follow-up visit.

6.5.1.4. Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

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

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

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

6.5.2. Prohibited 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.
- Anti-TNF or anti-IL-6 therapy (e.g., adalimumab, etanercept, infliximab, certolizumab, tocilizumab, golimumab).
- All biologics (e.g., rituximab, abatacept, interleukin-1 receptor antagonist).
- Intravenous immunoglobulin (IVIG).
- IV cyclophosphamide (oral cyclophosphamide is permitted).
- Plasmapheresis, leukapheresis.
- Any live or live attenuated vaccines. (Participants who require a live or live attenuated vaccine during the study should have belimumab discontinued prior to receiving the vaccine).

Note: 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.

6.6. Dose Modification

No dose modifications of belimumab are allowed. An exception is for a participant whose body weight changes within pre-defined criteria.

The participant must be weighed prior to dosing at each clinic visit and dosing frequency for the next period adjusted according to the criteria below. Site personnel should ensure they provide the participant with sufficient autoinjectors for possible home use prior to the next clinic visit. (See additional details in the SRM).

Part A		Part B and Optional Access Extension Phase		
Dosing cohort	**Dosing frequency**	**Body weight (BW)**	**Dosing frequency**	**Note**
Cohort 1 (BW ≥50 kg at baseline)	Every week	Remains ≥50 kg	Every week	
		Decreases to <50 kg	Every 10 days	Revert to every week if BW increases to ≥53 kg
Cohort 2 (BW ≥30 kg and <50 kg at baseline)	Every 10 days	Remains ≥30 kg and <50 kg	Every 10 days	
		Increases to ≥53 kg	Every week	Revert to every 10 days if BW decreases to <50 kg
		Decreases to <30 kg	Every 2 weeks	Revert to every 10 days if BW increases to ≥33 kg
Cohort 3[a] (BW <30 kg at baseline)	Every 2 weeks	Remains <30 kg	Every 2 weeks	
		Increases to ≥33 kg	Every 10 days	Revert to every 2 weeks if BW decrease to <30 kg

a. If BW drops below 15 kg at any time, suspend dosing and discuss with Medical Monitor to determine if participant should be withdrawn from the study.

6.7. Intervention after completion of Part A and Part B

Following the end of treatment at Week 52 or early withdrawal from the study, the participant will return to standard of care for SLE as determined by the investigator. Eligible participants who complete Part B (Section 6.7.1.1 and Section 6.7.1.2) may be enrolled into the optional access extension phase of the study from Week 52.

6.7.1. Optional Access Extension Phase

Access extension is an optional extension phase for 200908 to provide a mechanism for continued access to belimumab SC from Week 52 exclusively for eligible participants

(Section 6.7.1.1 and Section 6.7.1.2). The duration of this optional access extension phase depends on the age of participants when they are enrolled into the access extension phase and whether the circumstances leading to their eligibility change at any time (Section 6.7.1.3).

6.7.1.1. Optional Access Extension Phase Process

If per investigator's judgement a participant meets the eligibility criteria to enroll into the Optional Access Extension Phase, the Medical Monitor should be notified prior to enrolling any participant. The Investigator would be required to submit information related to their eligibility (see SRM for details), as determined by the specific inclusion and exclusion criteria (Section 6.7.1.2and Section 6.7.1.3). Eligibility information will be reviewed by the Medical Monitor and enrollment into the Optional Access Extension Phase can only proceed following Medical Monitor approval.

6.7.1.2. Optional Access Extension Phase Inclusion Criteria

1. Male or female participants who complete Week 52 visit of the 200908 study.
2. Age <18 years at completion of Week 52.
3. Documented evidence of clinical benefit in 200908 study per investigator's judgement.
4. Able to comply with clinic visits and required assessments.
5. Intravenous (IV) Benlysta not currently licensed for the pediatric use in the participant's country; **OR** documented evidence of the rationale for IV Benlysta not being suitable for this participant requiring continued treatment with belimumab SC (including but not limited to: medical reasons, significant logistical challenges, or other legitimate reasons [discuss with medical monitor]).
6. Participant eligibility agreed with the Medical Monitor prior to enrolling the participant into the optional access extension phase.
7. Participant signs and dates a written age appropriate assent form specific for the access extension phase (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 specific to the access extension.

6.7.1.3. Optional Access Extension Phase Exclusion Criteria

1. Female participant has positive urine pregnancy test at Week 52 visit.
2. Female participant wishes to become pregnant at or within 4 months of Week 52 visit.
3. Participant has experienced any change in his/her medical history that, per the investigator's judgement, continued administration of belimumab therapy would be contraindicated.
4. Participant received a live vaccine within 30 days prior to Week 52

6.7.1.4. Optional Access Extension Phase Withdrawal Criteria

A participant may be withdrawn from the optional access extension phase by the investigator and/or Sponsor for reasons including but not limited to:

1. Participant reaches the age of 18 years.
2. Depending on the condition the participant was eligible for the optional access extension phase:
    a. Belimumab SC (or IV) becomes licensed and commercially available for pediatric use in the participant's country.
    b. The reason for which IV Benlysta was not suitable for this participant is no longer valid.
3. Participant becomes pregnant.
4. Participant receives prohibited therapy (See Section 6.5.2).
5. Participant experiences unacceptable toxicity per investigator's judgement.
6. Participant participates in another interventional clinical trial.
7. Three Consecutive belimumab injections (see Section 6.4.2) or consecutive clinic visits (see Section 8.5) are missed.
8. Participant is no longer experiencing clinical benefit from belimumab per the documented medical judgement of the investigator.
9. Participant develops new or worsening of existing medical condition for which, in the opinion of the investigator or medical monitor, the risk of continued administration of belimumab outweighs clinical benefit to the participant; including liver chemistry stopping criteria (see Section 7.1.2) and/or IgG stopping criteria (see Section 7.1.1).
10. Sponsor becomes aware of new safety data that would preclude continued administration of SC belimumab.
11. It is the wish of the participant (or their legally acceptable representative) to withdraw for any reason.

Withdrawal from the optional access extension phase results in discontinued access to belimumab SC.

6.7.1.5. Optional Access Extension Phase Study Assessments and Procedures

- Study procedures and their timing during the optional access extension phase are summarized in the SoA (see Section 1.3.4).
- Visit frequency in the access extension is every 12 weeks (± 7 days) after Week 52 and for the entire duration of the optional access extension phase.
- Body weight should be checked at the beginning of each clinic visit and should be noted in the Investigators source documents. As the dosing frequency may change due to changes in participant's body weight, Section 6.6 should be followed for any

dose modifications. Any changes in body weight that lead to a change in dosing frequency should be noted and requested in the IWRS system (see SRM for details).

- No efficacy assessments are required during the optional access extension phase. The investigator will use their judgement to determine and continue to evaluate the clinical benefit from belimumab SC and pariticipants who are no longer experiencing clinical benefit will be withdrawn.
- Although routine safety laboratory monitoring is not required during the optional access extension phase, local laboratory assessments can be performed as part of the participant's routine evaluation or can be triggered by the investigator should a safety signal warrant further investigation per the investigator's judgement. Any abnormal results will be noted in the Investigator's source documents. The GSK Medical Monitor should be informed of any result that meets the safety stopping criteria (e.g. Liver Stopping Criteria in Section 7.1.2 and Grade 4 IgG level Section 7.1.1).
- Serious adverse event (SAE) definition and reporting during the optional access extension phase will follow the guidance in Section 8.9. During the optional access extension phase, SAEs will be reported to GSK via paper CRF only (see Section 10.3.4).
- For females of childbearing potential: urine pregnancy tests will be provided by sites at the scheduled visits in SOA (Section 1.3). Participants will be required to perform a urine pregnancy test every 4 weeks throughout the treatment period (1 onsite and 2 at home). Home urine pregnancy tests will also be provided for the 8-week and 16-week follow-up period. The results of urine pregnancy tests conducted at home will be recorded in the subject diary cards and stored as part of the investigator's source documents. Only positive pregnancy test results will be reported to GSK during the optional access extension phase and will follow the guidance in Section 8.9.5.
- Participants and caregivers will be provided with a subject diary card (refer to SRM for details). Participants must complete the subject diary card and bring it with them to each site visit. Compliance for all dosing, pregnancy testing and autoinjector malfunctions will be assessed and reviewed by the Investigator or site staff, with the participant/caregiver at each site visit. For any dosing or pregnancy testing conducted at the investigative site, participants or caregivers will complete the subject diary card. Results will not be reported and the completed subject diary card will be stored in the Investigator's source documents.
- 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. Participants and caregivers are required to return all used and unused autoinjector devices to the site, for their local disposal and destruction. All used autoinjectors should be placed in a sharps container and returned to site (see SRM for details). Any returned malfunctioning autoinjectors will be marked to distinguish them from the used autoinjectors (see SRM for details).
- Medical device incidents and malfunction reporting during the optional access extension phase will follow the guidance in Section 8.9.6 and Section 8.9.7.

- If participants withdraw from treatment at any time during the optional access extension phase, an early withdrawal (EW) visit should be completed. Additionally, 8 and 16-week follow-up visits are required via phone call to collect SAEs, and the results of home urine pregnancy test (if applicable) for female participants.

6.7.1.6. Optional Access Extension Phase Statistical Analyses and Reporting

- There are no formal statistical analyses being performed in the optional access extension phase.
- Summary of SAEs, pregnancies and medical device incidents reported in the safety database during the optional access extension phase will be provided in a synoptic clinical study report after conclusion of the optional access extension phase.

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 8.5 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 (see Section 6.4.2) or consecutive clinic visits (see Section 8.5) are missed.

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

- Become pregnant.
- Receive prohibited therapy (See Section 6.5.2)
- Experience unacceptable toxicity
- Participate in another interventional clinical trial
- Trigger liver chemistry stopping criteria (see Section 7.1.2) and/or IgG stopping criteria (see Section 7.1.1).

7.1.1. IgG Stopping Criteria

Any participant who has a Grade 4 IgG level, by the protocol defined Adverse Event and Laboratory Value Severity Grade Scale (see Appendix 2, Section 10.2.1), will have dosing with study agent withheld, and the appropriateness to continue study treatment must be discussed with the Medical Monitor before the next dose. Any participant who has a Grade 4 IgG level associated with a severe or serious infection will have study agent discontinued and should complete the follow-up assessments as described in the SoA (Section 1.3).

7.1.2. Liver Chemistry Stopping Criteria

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

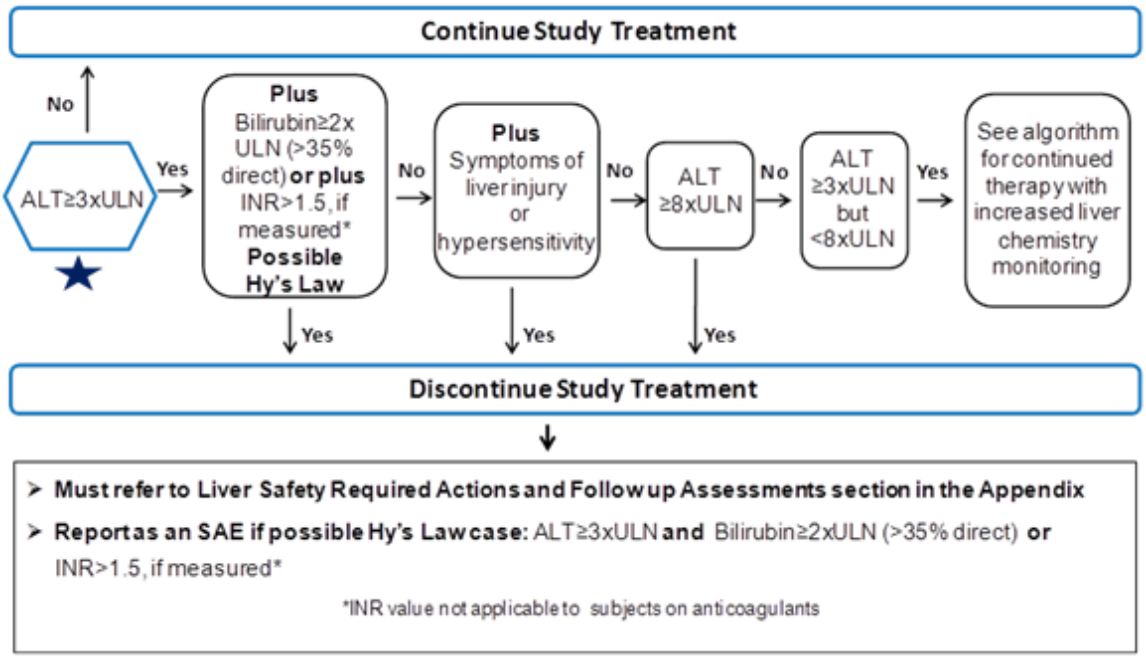
Discontinuation of study treatment is required when:

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

OR

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

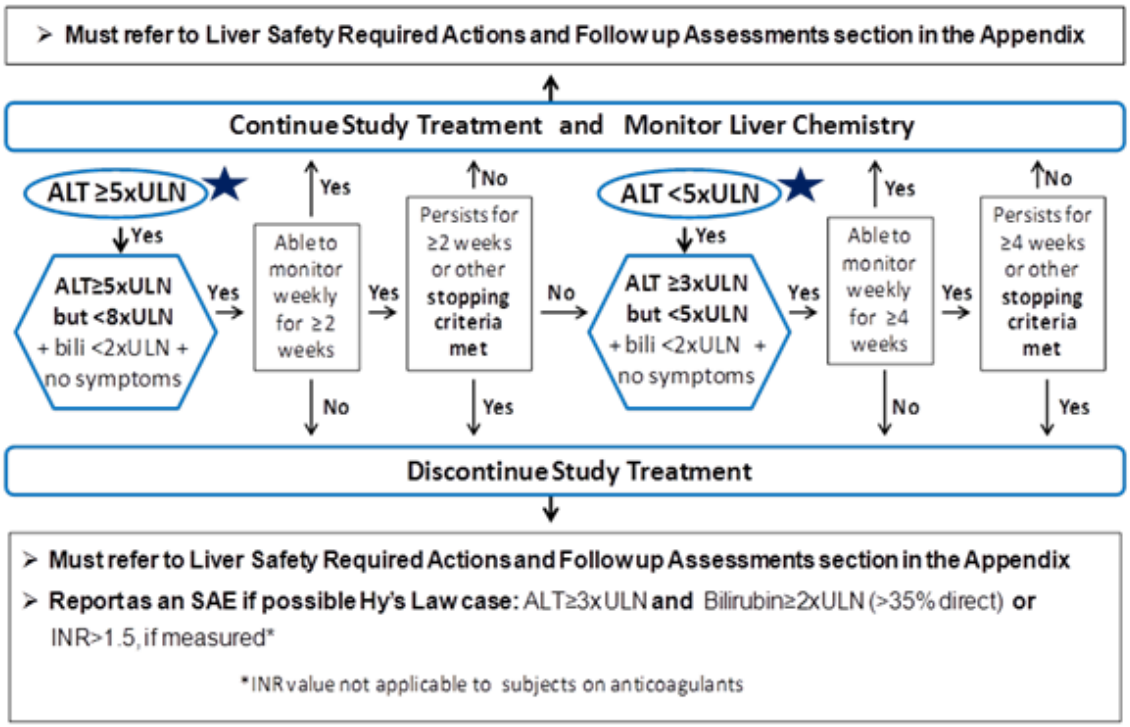
Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



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

See Appendix 5 for liver safety required actions and follow-up assessments.

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



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

See Appendix 5 for liver safety required actions and follow-up assessments.

7.1.2.1. Study Intervention Restart or Rechallenge After Liver Stopping Criteria Met

After liver stopping criteria are met, restart or rechallenge is not permitted.

7.1.3. Temporary Discontinuation

In the event of a participant experiencing an AE or SAE, the investigator may at their discretion choose to instruct the participant/caregiver to skip one or more scheduled administrations of belimumab. Please also refer to Section 6.4.2.

In the event a participant tests positive for COVID-19, or if no testing is available and a participant exhibits symptoms consistent with COVD-19, withhold dosing of belimumab until symptoms resolve and contact the Medical Monitor to discuss reinitiating belimumab treatment.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if participants are unwilling to return for the 8- and 16-week follow-up assessment then, if possible, an early withdrawal visit (as shown in the SoA - see Section 1.3 and Section 8.5) should be conducted at the time of withdrawal and every effort made to collect the results of a home pregnancy test (if applicable) and AEs 16 weeks after the last dose of belimumab.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant‘s parent/caregiver withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, her/his parent/caregiver may request destruction of any samples taken and not tested, and the investigator must comply and document this in the site study records.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (see Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed local guidelines.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples (see also Section 5.5).

8.1. Screening Assessments

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

Informed Consent

Informed consent will be obtained from the participant's parent/legally appointed representative 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. Participants who turn 18 years old during the course of the study will provide their own informed consent.

Participants who give written consent will enter a screening period of up to 35 days. A participant may have treatment assigned when all screening procedures have been completed and eligibility criteria confirmed.

Screening Assessments

During the screening period the following assessments will be performed:

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

Medical history/medication will be assessed as related to the exclusion criteria listed in Section 5.2. A complete medical history will be taken at the Screening Visit. Information

from the medical history is important to establish the baseline condition of the participant, and will impact the safety monitoring assessments during the study. Any significant medical conditions affecting the participant in the past 5 years should be recorded on the Medical conditions page of the eCRF. The history should include the following:

- Past or current conditions
- Prior surgical procedures
- Pharmacotherapy and chronic or current use of any medication or herbal preparation
- Prior use of belimumab
- Allergies and significant allergic reactions
- Significant infections, or history of recurrent infection, including urinary and respiratory tract infections
- Smoking history (current or previous smoker, number of cigarettes smoked per day)
- Cardiovascular medical history/risk factors (as detailed in the eCRF).

Pregnancy Test

A serum pregnancy test will be performed for females of child-bearing potential at the Screening Visit and a urine pregnancy test will be performed during each subsequent clinic visit. Refer to the pregnancy section (Section 8.9.5).

Full Physical Examination, Height, Weight, and Vital Signs

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

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

Electrocardiogram

A single 12-lead ECG will be obtained for screening purposes only as outlined in the SoA (see Section 1.3) 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.

Laboratory Tests

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

- Autoantibodies (anti-dsDNA, ANA), complement (C3, C4) and CRP
- HIV, hepatitis B and Hepatitis C screen
- Immunoglobulins (IgG, IgA, IgM)
- Urinalysis (including drug and alcohol screen)
- Hematology, PT/PTT and blood chemistry
- Urine protein:creatinine ratio
- Pregnancy test (serum)
- NOTE: To maintain the volume of blood collection with local guidelines, the screening assessments for particpants <30 kg will be split across 2 visits separated by a minimum of 2 weeks. There must also be a minimum of 2 weeks between the second screening and the Day 1 blood draws (see SRM for details). This may also apply to particpants ≥30 kg according to local guidelines.

Disease Activity Index

The SELENA SLEDAI (Appendix 9) will be performed at screening to assess the level of SLE severity.

Suicidality Assessment

Possible suicidal behavior or ideation will be assessed at screening (see also Section 5.2).

8.2. Baseline Assessments

Procedures at the Baseline Visit are listed in the SOA (Section 1.3). They include clinical assessments, laboratory tests, biomarkers and immunogenicity. 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 8.7 to Section 8.14 (and in the SRM).

8.3. Scheduled Visit Assessments

Procedures at the Scheduled Visits are listed in the SoA (Section 1.3). They include clinical assessments, laboratory tests, pharmacokinetics, biomarkers, and blood samples for immunogenicity. 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 8.7 to Section 8.14 (and in the SRM).

8.4. 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.

8.5. 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- 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.

8.6. 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).

8.7. Pharmacokinetic Assessments

- Blood samples will be collected for measurement of serum concentrations of belimumab as specified in the SoA (Section 1.3). 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.

8.8. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.8.1. 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.

8.8.2. 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.

8.8.3. Electrocardiograms

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

8.8.4. Clinical Safety Laboratory Assessments

- A central laboratory will be used in this study.
- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 60 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- Laboratory toxicity will be graded using the Adverse Event and Laboratory Value Severity Grading Table (Appendix 2, Section 10.2.1). The Table is based upon publicly available Tables from the National Institute of Allergy and Infectious Disease Division of Microbiology and Infectious Diseases

(www.niaid.nih.gov) and Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (U.S. Department of Health and Human Services, 2010).

- Note: If a laboratory value is reported that requires withholding of further dosing, the site personnel must contact the parent/caregiver promptly to ensure no further injections are administered until reviewed with the investigator if the next administration would be away from the clinic.

8.8.5. Suicidal Ideation and Behavior Risk Monitoring

Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation [Bachen, 2009; Timonen, 2003; Stenager, 1992]. Investigators are reminded of the importance to clinically assess for suicidality at every visit given that SLE patients are (or autoimmune disease patients may be) at increased risk of suicidal behavior and/or ideation. There have been reports of suicidal ideation or behavior symptoms, as reported in the product label in some patients being treated with belimumab for SLE. A high risk of suicidality is exclusionary in this study.

Participants being treated with belimumab should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to withholding belimumab dosing and investigating further in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants being treated with belimumab should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

If evidence of suicidal behavior or ideation by a participant is detected at any visit, it is recommended that the Investigator consider mental health consultation or referral. The Medical Monitor should be notified when these events occur. In addition, the possible suicidality related event (PSRAE) form must be completed in the eCRF in Part A and B of the study.

8.9. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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 or study 200908 (see Section 7).

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

- All SAEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated

procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

- All AEs will be collected from the start of treatment until the follow-up visit in Part B of the study 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 on the Medical History/Current Medical Conditions section of the CRF, and not within the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in 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 AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.9.2. Method of Detecting AEs and SAEs

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

8.9.3. 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 non-serious and serious AEs of special interest (AESI) (i.e., post-injection systemic reactions and hypersensitivity reactions, infections, malignancies, and depression/suicidality/self-injury) will be followed until the event is resolved, 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 Appendix 3.

8.9.4. 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.

8.9.5. Pregnancy

- If a pregnancy in a female participant is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- A pregnancy is not considered to be an SAE, although abnormal pregnancy outcomes or complications (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.
- There is no requirement to collect pregnancy information from female partners of male participants.

8.9.6. Medical Device Incidents (Including Malfunctions)

Medical devices (i.e. belimumab autoinjectors) are being provided for use in this study for the purposes of administering belimumab from a pre-filled syringe contained within an autoinjector device. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 6.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.9.3 and Appendix 3 of the protocol.

8.9.6.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device 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 incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

- The method of documenting Medical Device Incidents is provided in Appendix 6.

8.9.6.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE or SAE will be followed and reported in the same manner as other AEs (see Section 8.9.3). This applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.9.6.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device Incident Report Form and Device Malfunction/Failure Reporting Form will be sent to the sponsor by email (see SRM for details). If email is unavailable, then a paper form should be utilized.
- The Device Malfunction/Failure Reporting Form will be sent to the sponsor along with the Medical Device Incident Form (see SRM).

8.9.6.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to 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.
- 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 incidents to the IRB/IEC.

8.9.7. Medical Device Malfunctions

Medical devices (Belimumab Autoinjector) that are provided for use in this study for the purposes of self-administration of study treatment may malfunction during use (e.g., parts missing, device leaking, needle bent). The information provided in this section applies to occurrence and reporting of device malfunctions that are NOT associated with an AE/SAE.

If when using an autoinjector, the participant experiences a device malfunction, the participant or their caregiver should stop using the device and SKIP additional attempts and not re-inject for that week's belimumab dose. (See Section 6.4.2.1 for additional

instruction regarding administration of study treatment following a device malfunction). Note: if a malfunction has been noticed before any attempt to use it e.g., cap missing, then the autoinjector can be set aside for return to GSK and a new autoinjector can be used.

The participant or caregiver should record the malfunction in their injection diary and contact the site the same day or as soon as possible to report the device malfunction. The study site should record the malfunction on the Device Malfunction/Failure Reporting Form and forward the information to GSK as described on the form as soon as possible (see SRM). The participant should return the malfunctioned device to the study site at the next scheduled visit for shipment back to GSK for evaluation.

8.10. Efficacy Assessments

The SELENA SLEDAI (Appendix 9) will be perfomed at the visits indicated in the SOA (Section 1.3).

8.11. Treatment of Overdose

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

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

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

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

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

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

8.12. Pharmacodynamics and Biomarkers

Pharmacodynamic parameters and biomarkers will be evaluated in this study according to the SOA (Section 1.3). Laboratory evaluations will include the following:

- Autoantibodies: anti-dsDNA, ANA
- Serum immunoglobulin isotypes: IgG, IgM, IgA.
- Serum complement (C3, C4).

- Peripheral lymphocytes including B lymphocytes (CD20+, CD20+/27+ memory, CD20+/27– naïve, CD19+/27br/38br 'SLE subset').
- BLyS protein (analyzed at a laboratory contracted by GSK other than the central laboratory).

Samples will be collected pre-dose when taken at dosing visits. All biomarker samples will be analyzed by the central laboratory unless otherwise stated.

8.13. Genetics

Genetics are not analyzed in this study.

8.14. Immunogenicity

The presence of antibodies to belimumab will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). These samples will be analyzed at a laboratory contracted by GSK other than the central laboratory).

8.15. 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, safety, and PD of belimumab during Parts A and B, and as such no formal statistical hypothesis testing is planned.

9.2. Sample Size Determination

Assuming a 20% screen-failure rate, it is expected that 36 participants will need to be screened in order that approximately 28 participants will be enrolled (treated with at least one dose of study treatment) aiming for 24 evaluable participants at Week 12. Enrollment and study withdrawals will be closely monitored and if there is an impact on continuation of participants in the study due to the Coronavirus SARS-CoV-2 (COVID-19) pandemic, more than 36 participants may be screened and more than 28 may need to be enrolled, to ensure the ability to achieve the evaluable target at Week 12.

The sample size of 24 participants and the specified sampling schedule allow estimation of central clearance and volume of distribution with a 95% confidence interval within 60% and 140% [Wang, 2012] with a power of 99.9% and 99.7%, respectively (mean 95% confidence intervals were 83.8-116.2% and 80.5-119.5%, respectively). The 95% CI were derived by simulating pediatric PK data and estimating clearance and volume of distribution with a population PK model for 2000 trial replicates (power estimates based on 1843 model estimates with successful covariance step). The following assumptions were used: (i) the simulations were based on participant data and the population PK parameters from pediatric IV study BEL114055 (see Section 2.2.1) augmented by the

subcutaneous absorption parameters obtained from adult SC population PK model [Struemper, 2018]; (ii) PK data for 24 participants were simulated for Part A of the study only (including the 8-week follow-up visit); (iii) the population PK model used for parameter estimation was a linear one-compartment model with first-order absorption.

Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants whose parent/caregiver sign the ICF
Enrolled	All participants assigned treatment by the IWRS.
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 for whom at least one post belimumab treatment PK sample was obtained and analyzed.

9.3. Statistical Analyses

9.3.1. Pharmacokinetic Analyses

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

Endpoint	Statistical Analysis Methods
Primary	Endpoints: Observed belimumab concentrations at Week 12. Steady-state PK parameters: Cavg (AUC), Cmax, Cmin (based on population PK estimates). Analysis: Descriptive statistics will be used to summarize the observed belimumab concentrations at Week 12. Descriptive statistics will be used to summarize the steady-state PK parameters: Cavg (AUC), Cmax, Cmin (based on population PK estimates).

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

9.3.2. Safety Analyses

All safety analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Secondary	Endpoints: Incidence of adverse events, serious adverse events, and adverse events of special interest (AESI) through Week 52. Analysis: Descriptive statistics will be used to summarize AEs, SAEs, and AESIs. The frequency of AEs will be tabulated by MedDRA system organ class (SOC) and preferred term.

9.3.3. Pharmacodynamic Analyses

All pharmacodynamic analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Secondary	Endpoints: Change from baseline in biomarkers (C3/C4, anti-dsDNA, B cell subsets, and immunoglobulins) at Weeks 12 and 52. Analysis: Descriptive statistics will be used to summarize change from baseline in biomarkers (C3/C4, anti-dsDNA, B cell subsets, and immunoglobulins) at Weeks 12 and 52.

9.3.4. Other Analyses

Other analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Other	Endpoint: Percent of subjects with a ≥ 4 point reduction from baseline in SELENA SLEDAI at Weeks 12 and 52. Analysis: Descriptive statistics will be used to summarize the number and percentage of subjects with a ≥ 4 point reduction from baseline in SELENA SLEDAI at Weeks 12 and 52.

Other biomarker analyses, efficacy analyses, and safety analyses will be described in the reporting and analysis plan.

9.4. Interim Analyses

No formal interim analyses are planned. In-stream review of the safety and PK data will be performed by the study Medical Monitor, members of the GSK Safety Review Team (SRT), and the GSK Pharmacokinetics Review Team (PRT).

9.4.1. GSK Safety Review Team (SRT)

The study Medical Monitor and members of the GSK SRT will perform in-stream review of all safety data throughout Part A and Part B of the study and make and communicate recommendations as appropriate. SAEs reported during the optional access extension phase will not be part of this in-stream review.

9.4.2. GSK Pharmacokinetics Review Team (PRT)

The GSK PRT will include the study Medical Monitor, Clinical Science Lead, Statistician, Safety Scientist/Physician, and Pharmacokineticist. Additional GSK scientists/physicians may also be invited to assist the PRT with data reviews. The PRT will review all available PK data after the first 6 participants in Cohort 1 (≥50 kg) or Cohort 2 (≧30 kg to <50 kg) have completed Week 12. For Cohort 3 (<30 kg), preliminary PK data will be reviewed by the PRT based on a data cut triggered by the first Cohort 3 participant having completed Week 12. The primary objective of the PRT meetings will be to either confirm the initial dose or to recommend an adjustment in dosing frequency if a substantial difference in exposure is observed compared to exposure in adult SLE participants receiving 200 mg SC belimumab every week. Recommendations will be made regarding dose confirmation or adjustment. The recommendations of the PRT will be summarized and distributed to study team members and Investigators.

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 ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent 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.
- The medical record must include a statement that written informed consent was obtained before the participant entered the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- Participants must provide their own consent if they reach 18 years old during the course of the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

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.
- 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. 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.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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.
- 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.

10.1.8. Source Documents

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

10.1.9. Study and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
  - 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 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Calcium	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin
	Calcium corrected for Albumin Inorganic Phosphate	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein

Laboratory Assessments	**Parameters**			
	Carbon dioxide	Magnesium	Alkaline phosphatase	Albumin
	Glucose (nonfasting)		Gamma glutamyl transpeptidase (GGT)	Creatinine
	Uric acid	Blood urea nitrogen (BUN)	BUN/creatinine ratio	Estimated Creatinine Clearance/GFR (Schwartz[2])
Routine Urinalysis	• pH, glucose, protein, blood, ketones, occult blood by dipstick • Microscopic examination (if blood or protein is abnormal)			
Biological markers	• BLyS protein • Serum complement (C3 and C4) • C-Reactive Protein (CRP) • Peripheral lymphocytes including B lymphocytes (CD20+, CD20+/27+ memory, CD20+/27– naïve, CD19+/27br/38br 'SLE subset').			
Immunoglobulins	• Serum immunoglobulin isotypes: IgG, IgM, IgA			
PK	• Blood collection			
Immunogenicity	• Blood collection			
Autoantibodies	• ANA titer, Anti-dsDNA			
Other Screening Tests	• Screening pregnancy • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Highly sensitive human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], 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 7.1.2 and Appendix 5. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized 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. 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
Hemoglobin	> 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
Methemoglobin	5.0-10.0 %	10.1-15.0 %	15.1-20.0 %	> 20%
Lymphocyte count**	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L

(continued)

*ULN = Upper Limit of Normal

**Lymphopenia calculated from CTCAE table

Adverse Event and Laboratory Value Severity Grade Table (continued)

CARDIOVASCULAR	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac Arrhythmia	-	Asymptomatic/transient; dysrhythmia; no treatment req	Recurrent/persistent dysrhythmia. Symptomatic; treatment req	Unstable dysrhythmia hospitalization and treatment required
Hypotension	Transient orthostatic hypotension, no treatment	Symptoms correctable with oral fluid treatment	IV fluid req, no hospitalization req	Hospitalization req
Hypertension	Transient, increase > 20 mm/Hg; no treatment	Recurrent; chronic increase > 20 mm/Hg, treatment req	Acute treatment req; out subject hospitalization possible	Hospitalization req
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion, pain, ECG changes	Tamponade OR pericardiocentesis OR surgery req
Hemorrhage, 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				
Hypokalemia	3.0-3.4 meq/L	2.5-2.9 meq/L	2.0-2.4 meq/L	< 2.0 meq/L
Hyperkalemia	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)				
Hypocalcemia	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				
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	< 30 mg/dL
Hyperglycemia (nonfasting & no prior diabetes)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	> 500 mg/dL
Triglycerides	151-399 mg/dL	400-750 mg/dL	751-1200 mg/dL	> 1200 mg/dL
Creatinine	> 1.0-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0-6.0 x ULN	> 6.0 x ULN

Adverse Event and Laboratory Value Severity Grade Table (continued)

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

(continued)

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

Adverse Event and Laboratory Value Severity Grade Table (continued)

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

Adverse Event and Laboratory Value Severity Grade Table (continued)

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

URINALYSIS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proteinuria				
Dispstick 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
Hematuria	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	Localized urticaria	Generalized 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 Hospitalization
Paresthesia (burning, tingling, etc)	Mild discomfort; no treatment needed	Mod discomfort non-narcotic analgesia req	Severe discomfort; OR narcotic analgesia req with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia
Neuro-motor	Mild weakness in muscle of feet but able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and mod proximal weakness ie, in hands interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheelchair because of muscle weakness
Neuro-sensory	Mild impairment sensations, (ie, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment mod de-sensation, (ie, of vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical.	Severe impairment (dec or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	Sensory loss involves limbs and trunk

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any 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 <u>Meeting</u> the AE Definition
• 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 judgement of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

- Results in death

- Is life-threatening

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

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during 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.

Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

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 (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF in Parts A and B of the study.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

  Other measures to evaluate AE and SAE may be utilized (see Appendix 2 - Adverse Event and Laboratory Value Severity Grade Tables).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF in Parts A and B.
- 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

- In Parts A and B , the primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After Part B of the study is completed at a given site, the electronic data collection tool will be locked 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 the SRM.

SAE Reporting to GSK via Paper CRF

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

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

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A female 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, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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 enrollment.

10.4.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized 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 (estrogen- 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 which 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. Male condom and female condom should not be used together (due to risk of failure with friction)

Female Participants who become pregnant

- Any female participant who becomes pregnant while participating will discontinue study intervention and be withdrawn from the study.
- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- 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 fetal 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 a medical reason will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which 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.

10.5. Appendix 5 Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart Guidelines

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology

Phase III-IV liver chemistry stopping criteria and required follow-up assessments

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

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 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize 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 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Fractionate bilirubin, if total bilirubin≥2xULN • 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. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • 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 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; 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. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. 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 III-IV 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 normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of acetaminophen-adduct in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009; 37:1779-84.

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 subjects. J Clin Microbiol. 2005;43(5):2363–2369.

10.5.1. Restart Following Transient Resolving Liver Stopping Events Not Related to Study Intervention

After liver stopping criteria are met, restart or rechallenge is not permitted, see Section 7.1.2.1.

10.6. Appendix 6: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

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 for the list of GSK medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study intervention is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • 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 an incident. This includes any amendment to the device design to prevent recurrence.

10.7. Appendix 7: Country-specific requirements

Country specific changes in Protocol Amendment 01 apply to Investigator Sites in Japan only.

Summary of Country Specific Changes and Rationale

Section	Global Wording	New Country Specific Wording	Rationale

Inclusion criterion #7	• 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.	Of the allowed options for birth control in inclusion criterion #7, the following are not approved and cannot be used in Japan:
		• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
		• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
		  • Oral
		  • Intravaginal
		  • Transdermal
		  • Injectable
		• Progestogen-only hormone contraception associated with inhibition of ovulation
		  • Oral
		  • Injectable
			To exclude contraceptive methods not approved in Japan

Exclusion crierion #10	Have acute or chronic infections requiring management, as follows: • Currently on any suppressive therapy for	Participants are excluded if they have: • symptoms or signs which suggest active TB from medical	To exclude participants with evidence of active TB

Section	Global Wording	New Country Specific Wording	Rationale
	a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria). • Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) for infection within 60 days of Day 1.	history or on examination • recent close contact with a patient with active TB; • Evidence indicating TB infection on Interferon-gamma release assay (QuantiFERON, T-SPOT) or tuberculin skin test conducted within 5 weeks before the first dose of study treatment; • Chest X-ray or CT scan) taken within 3 months before first dose of study treatment showing evidence indicating active TB.	

10.8. Appendix 8: Country-specific Protocol Amendment 02 Requirements

Country specific changes in Protocol Amendment 02 apply to Investigator sites in the Netherlands only.

Summary of Country Specific Changes and Rationale

Section	**Global Wording**	**New Country Specific Wording**	**Rationale**
7.2 Participant Discontinuation/Withdrawal from the Study	• A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.	• With younger children, careful attention should be paid to signs of resistance to (further) participation. In the event of signs of resistance, the participant will be permanently discontinued from the study. The Netherlands Association for Paediatric Medicine's (NVK) code of conduct relating to expressions of objection by minors participating in medical research will be adhered to.	To incorporate Netherlands required wording for studies involving children.
8.9.4 Regulatory Reporting Requirements for SAEs	• 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	• The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of	To exclude participants with evidence of active TB

Section	Global Wording	New Country Specific Wording	Rationale
	authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.	maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.	

10.9. Appendix 9: ACR Criteria

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

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

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

10.10. Appendix 10: SELENA SLEDAI Disease Assessment Scale

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

Wgt.	Descriptor	Definition
8	Seizure	Recent onset (last 10 days). Exclude metabolic, infectious drug cause, or seizure due to past irreversible CNS damage.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	Visual Disturbance	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exudate of hemorrhage in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes.
8	Cranial Nerve Disorder	New onset sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	CVA	New onset of CVA(s). Exclude arteriosclerosis or hypertensive causes.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	Arthritis	More than 2 joints with pain & signs of inflammation (ie, tenderness, swelling or effusion).
4	Myositis	Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	Urinary Casts	Heme-granular or red blood cell casts.
4	Hematuria	> 5 red blood cells/high power field. Exclude stone, infection, or other causes.
4	Proteinuria	New onset or recent increase of more than 0.5 g/24 hours.
4	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	Rash	New or ongoing inflammatory lupus rash.
2	Alopecia	New or ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
2	Mucosal Ulcers	New or ongoing oral or nasal ulcerations due to active lupus.
2	Pleurisy	Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.
2	Pericarditis	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
2	Low Complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	Increased DNA Binding	> 25% binding by Farr assay or above normal range for testing laboratory.
1	Fever	> 38°C. Exclude infectious cause.
1	Thrombocytopenia	< 100,000 platelets/mm^3
1	Leukopenia	< 3,000 white blood cells/mm^3. Exclude drug causes.
	TOTAL SCORE	**(Sum of weights next to descriptors marked present)**

10.11. Appendix 11: Abbreviations and Trademarks

aCL	Anticardiolipin
ACR	American College of Rheumatology
ADA	Anti drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine amininotransferase
ANA	Anti-nuclear antibody
AST	Aspartate aminotransferase
AUC	Area under the curve
BLyS	B lymphocyte Stimulator
BW	Body weight
C3/C4	Complement factor C3 and C4
Cavg	Average concentration
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CiC	Child in care
Cmax	Maximum concentration
Cmin	Minimum concentration
CNS	Central nervous system
COVID-19	Coronavirus SARS-CoV-2 (**CO**rona **V**irus **D**isease -20**19)**
CPK	Creatinine phosphokinase
CrCl	Creatinine clearance
CRP	C-reactive protein
CRF	Case report form
dL	Deciliter
dsDNA	Double stranded deoxyribonucleic acid
eCRF	Electronic case report form
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HB	Hepatitis B
HBsAg	Hepatitis B surface antigen
HBc	Hepatitis B core
HGS	Human Genome Sciences, Inc
HIV	Human immunodeficiency virus
hpf	High power field
IA	Intraarticular
IB	Investigator's Brochure
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IL-6	Interleukin-6

IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to Treat
IUD	Intrauterine device
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWRS	Interactive web response system
kg	Kilogram
LDH	Lactate dehydrogenase
mg	Milligram
mL	Milliliter
MCID	Minimally clinically important difference
µg	Microgram
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MMF	Mycophenolate mofetil
MRI	Magnetic Resonance Imagery
MSDS N/A	Materials Safety Data Sheet Not applicable
NSAIDs	Non-steroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	By mouth (per os)
PRINTO	Pediatric Rheumatology International Trials Organization
PRT	Pharmacokinetic Review Team
PT	Prothrombin time
PTT	Partial thromboplastin time
QW	Once a week
Q10D	Every 10 days
Q2W	Every 2 weeks
RA	Rheumatoid arthritis
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SC	Subcutaneous
SELENA	Safety of Estrogen in Lupus Erythematosus National Assessment
SFI	SLE Flare Index
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
SRT	Safety Review Team
TACI Fc	Transmembrane activator attached to the Fc portion of an immunoglobulin
TB	Tuberculosis
TNF	Tumor Necrosis Factor
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
BENLYSTA
BLyS
LymphoStat-B

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA

10.12. Appendix 12: Protocol Amendment History

Amendment 3 14-Jul-2021

Overall Rationale for the Amendment:

The purpose of this amendment is to add an optional access extension phase post Week 52 exclusively for eligible participants who complete Part B of the study (e.g., participants from countries where the IV formulation is not approved for pediatric use; or participants in whom IV Benlysta is not suitable due to medical reasons or significant logistical challenges; see Section 6.7.1 for full eligibility criteria). At the time of the 200908 protocol development, belimumab IV formulation was expected to be licensed and available for SLE patients aged 5 years and older following completion of the study in all countries where the 200908 study is conducted. Currently in Mexico, belimumab IV is not approved for pediatric use in SLE patients. Additionally, in countries where IV Benlysta is approved, it might not be suitable for individual participants as post study treatment due to medical reasons or significant logistical difficulties. Therefore, this optional access extension phase has been introduced to provide a mechanism for continued access to belimumab SC from Week 52 onwards for eligible participants. Participants who are enrolled into the optional access extension phase will be withdrawn from treatment if they reach the age of 18 years or if Belimumab SC or IV becomes licensed and commercially available for pediatric use in the participant's country (see Section 6.7.1.4for full withdrawal criteria).

Section # and Name	Description of Change	Brief Rationale
Synopsis	Added information regarding optional access extension phase and updated wording to clarify items only pertaining to Part A and Part B	The optional access extension phase was added to provide a mechanism for continued access to belimumab SC from week 52 onwards for eligible participants. This was added to study design and clarified items only pertaining to Part A and Part B
Section 1.2, Schema	Updated to include optional access extension phase	The Schema was updated to reflect the added optional extension phase
Section 1.3, Schedule of Activities	Added wording in Note for Section 1.3.1 and Section 1.3.2 for optional access extension phase. Added a note to Section 1.3.3 to clarify that 8- and 16-week follow-up visits are NOT required for participants who are eligible for and are enrolled	List of the activites during the newly added optional access extension phase was added to the SOA. Wording was changed in the impacted sections of Part A and Part B.

Section # and Name	Description of Change	Brief Rationale
	into the optional access extension phase. Added new table in Section 1.3.4 with activities in optional access extension phase	
Section 4.1, Study Design	Added information regarding optional access extension phase and updated wording to clarify applicability to Part A and B	The optional access extension phase was added to the study design to provide a mechanism for continued access to belimumab SC from week 52 onwards for eligible participants.
Section 4.4, End of Study	Updated wording to clarify applicability to Part A and B	To clarify items pertaining only to Parts A and B
Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria	Added wording to clarify applicability to Part A and B	To clarify items pertaining only to Parts A and B
Section 6.4.1, Compliance with Subcutaneous Administration of Belimumab	Added subheading for “Parts A and B” and wording to clarify applicability to Part A and B	To clarify items pertaining only to Parts A and B
Section 6.6, Dose Modification	Added optional access extension phase to Part B dose modification instructions	To clarify dose modification instructions during the optional access extension phase
Section 6.7, Intervention after the End of the Study	Added wording to Section 6.7 for eligibility in the optional access extension phase. Added new section for the Optional Access Extension Phase (6.7.1) and subsections for process (6.7.1.1), inclusion criteria (6.7.1.2), exculsion criteria (6.7.1.3), withdrawal criteria (6.7.1.4), and study assessments and procedures (6.7.1.5), and statistical analyses and reporting (6.7.1.6)	Clarified that for eligible participants, the optional access extension phase was added to provide a mechanism for continued access to belimumab SC from week 52 onwards. The added sections clarify the process for enrolling eligible participants into the access extension phase, eligibility criteria, withdrawal criteria, study assessments and procedures and statistical analyses and reporting in the access extension phase.

Section # and Name	Description of Change	Brief Rationale
Section 8.8.5, Suicidal Ideation and Behavior Risk Monitoring	Added wording to clarify data collection for Part A and B	To clarify items pertaining only to Parts A and B
Section 8.9.1, Time Period and Frequency for Collecting AE and SAE information	Added wording to clarify AE collection through follow-up in Part B	To clarify AEs will only be collected in Parts A and B of the study
Section 9.1, Statistical Hypotheses	Updated wording to clarify applicability to Part A and B	To clarify items pertaining only to Parts A and B
Section 9.4.1, GSK Safety Review Team	Updated wording to clarify applicability to Part A and B and to clarify that SAEs reported during the optional access extension phase will not be part of the GSK Safety Review Team (SRT) in-stream review.	To clarify items pertaining only to Parts A and B
Section 10.3.3, Recording and Follow-up of AE and SAE	Updated wording to clarify applicability to Part A and B	To clarify items pertaining only to Parts A and B
Section 10.3.4, Reporting of SAE to GSK	Updated wording to clarify applicability to Part A and B	To clarify items pertaining only to Parts A and B

Amendment 2 24-APR-2020

Overall Rationale for the Amendment:

This amendment adjusts the protocol in response to the COVID-19 pandemic. The purpose of this amendment is to provide flexibility to protocol specified visits and assessments in accordance with guidance from regulatory agencies, while maintaining trial and data integrity.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 4.1 Overall design; 9.2 Sample Size Determination	Flexibility added to allow more than 36 participants to be screened and additional participants enrolled to achieve the original number of 24 evaluable participants.	The flexibility has been added to allow for the possibility of higher than anticipated withdrawals due to the COVID-19 pandemic.
1.2 Schema	Schmatic updated to clarify study visits for Cohort 2 are 10 days apart.	The schematic had the same visits for all 3 cohorts with description indicating the different visit schedule for the 10 day dosing cohort. The schematic was updated to align with the legend.
1.3.1 SOA Cohorts 1 and 3, 1.3.2 SOA Cohort 2 and	Visit windows were widened.	To provide some more flexibility due to the COVID-19 pandemic, while maintaining the 3 different dosing schedules, visit windows were increased.
1.3.3 SOA Part B All participants	The PK sampling and belimumab administration windows were widened.	To provide some more flexibility due to the COVID-19 pandemic, while maintaining the 3 different dosing schedules, PK sampling and belimumab administration windows were increased.

Section # and Name	Description of Change	Brief Rationale
2.3.1 Risk Assessment; 5.2 Exclusion criteria	'to any of the excipients of the study drug' added	To further clarify that a history of anaphylactic reaction also includes any of the excipients of the study drug.
4.1 Overall design; 9.4.2 GSK Pharmacokinetics Review Team	The number of participants that triggered a data review by the pharmacokinetic team was changed from after the first 12 participants, to now after the first 6 participants in Cohorts 1 or 2 have completed Week 12.	If recruitment is slow, to ensure an early PK data review to determine whether a change in frequency of dosing is required.
7.1.3 Temporary Discontinuation	Addtion of requirement to temporarily discontinue study medication for COVID-19 positive participants or if no testing is available for those exhibiting symptoms consistent with COVID-19	Clarification of protocol specific procedures to be followed for COVID-19 positive participants or those exhibiting symptoms of COVID-19 with regards to study medication.
10.8 Country Specific Requirements	Addition of Netherlands country specific requirements regarding discontinuation/withdrawal from the study and regulatory reporting requirements for SAEs	To comply with local requirements in the Netherlands for studies involving children.
Throughout the protocol	Administrative edits	Minor edits such as updating the list of abbreviations.

Amendment 1 24-Jul-2019

Overall Rationale for the Amendment:

This amendment adjusts and clarifies the number of planned participants to ensure compliance with regulatory commitments. Additionally the following changes have been added: modification of the exclusion criterion pertaining to hepatitis B status to align with current GSK guidance, allowance for in clinic 16-week follow-up, splitting of screening testing for lower weight participants to ensure blood volume collection remains within local guidance, and other wording changes for clarification. Furthermore, an Appendix has the Japan country specific requirements that have been added to the inclusion/exclusion criteria.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; 4.1 Overall design; 9.2 Sample Size Determination	Adjustment and clarification of number of participants – now approximately 36 screened, 28 enrolled aiming for 24 evaluable.	The number of participants screened and enrolled has been increased to allow for 24 evaluable participants
1.3.1 SOA Cohorts 1 and 3; 1.3.2 SOA Cohort 2; 8.1 Screening – Lab tests	Note added to indicate screening lab tests for participants < 30kg will be split over 2 visits separated by at least 2 weeks.Second screening and Day 1 visit also to be separated by 2 weeks.May also apply to particpants ≥ 30kg per local requirements.	To allow for compliance with local guidance on limit to blood volume collected in single draw.
1.3.1 SOA Cohorts 1 and 3, 1.3.2 SOA Cohort 2 and 1.3.3 SOA Part B All participants	Location of pregnancy testing at Week 16 follow-up clarified	The 16-week follow-up may be perfomed at an in clinic visit according to local requirement.
1.3.1 SOA Cohort 1 and 3	Addtion of pregnancy test at Day 8 and Day 15	To ensure pregnancy is ruled out at each clinic visit.
1.3.2 SOA Cohort 2	Addtion of pregnancy test at Day 11 and Day 21	To ensure pregnancy is ruled out at each each visit.
2.2.2 Benefit Assessment	Insertion of 'in adults' to description of IV and SC trial results description	To clarify the results are from adult data

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Change in exclusion criterion for hepatitis B status #23	To comply with GSK Hepatology Board guidance
6.1.1.1	Video link to guidance on use of autoinjector will be provided to site personnel only	To clarify the video is for reference by site personnel only
6.4.1 Compliance	Requirement to record estimated proportion of a partially administered dose in the patient diary card removed Removal of 'self' as prefix to injection diary	Estimation of the proportion of a partially administered dose is no longer required. To acknowledge injection with be given by parent/caregiver to participants under 12 years old.
6.4.2 Missed doses	Rules to follow if a dose is missed have been modified.	Clarification of wording to minimise gaps in scheduled dosing while maintaining weekly gap between doses.
6.5.1 Permitted Concomitant therapy	Re-wording of guidance on use of concomitant anti-malarials, steroids and NDSAIDs.	To provide clearer guidance to investigator on permitted concomitant medication throughout the study.
8.1.1 Treatment of Overdose	Definition of belimumab overdose has been removed.	The dosage of belimumab considered an overdose has not been defined.
10.7 Country Specific Requirements	Addition of Japan country specific requirements regarding inclusion/exclusion criteria	To comply with local requirements in Japan
11 References	Addition of 2 new references	References added to support included statements.

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