TITLE PAGE

Protocol Title: An open-label, randomized, parallel group, single dose study to investigate the PK and safety of belimumab 200 mg intravenous and 200 mg subcutaneous via auto-injector in Chinese healthy participants.

Protocol Number: 209629/Amendment 01

Compound Number: GSK1550188

Study Phase: Phase 1

Short Title: Single dose study to investigate the PK and safety of belimumab 200 mg intravenous and 200 mg subcutaneous via auto-injector in Chinese healthy participants

Sponsor Name and Legal Registered Address:

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

Sponsor Contact Address:

GlaxoSmithKline (Shanghai) Research & Development Limited

No. 18, 999 HuanKe Road, Zhangjiang, Pudong

Shanghai 201203, China

Medical Monitor Name and Contact Information

This information will be provided in the Study Reference Manual (SRM).

Approval Date: 27-JUN-2019

SPONSOR SIGNATORY:

PPD

27-Jun-2019

Sun Fang
Senior Clinical Research Physician

Date

As Delegated by

Nathan Chen
Therapeutical Area Head, Immuno-inflammation
Research & Development
GlaxoSmithKline China

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment01	*27-Jun-2019*	*2018N385241_01*
Original Protocol	*18-Mar-2019*	*2018N385241_00*

Amendment 01 27-June-2019

Overall Rationale for the Amendment: The changes made aim to increasing operational feasibility and consistency with clinical study practice at the study site. Key changes including:

- Time of pre-dose blood sampling changed from point to a time window.
- Changing method to collect blood pressure, body temperature; and pulse rate is replaced by heart rate to better reflect clinical practice.
- Correction of other inconsistency and typos.

Section # and Name	**Description of Change**	**Brief Rationale**
8 STUDY ASSESSMENTS AND PROCEDURES	In the table of Time assessment Window, change "-4 hrs" to "Any time before dosing" Change note "a" to "Including physical examinations, vistal signs, local tolerance, ECG, clinical safety laboratory assessments and other applicable tests". Delete superscripts and notes of "b" and "c" and make corresponding changes.	Change from time point to a time window of pre-dose blood sampling to increase site operation feasibility. To describe safety evaluation in detail. Delete urine tests that will not be done on Day 1 and Day 2-7.
8.5 Pharmacokinetics	Delete "-4 h" in the first paragraph	Ensure consistent with Section 8.
5.2 Exclusion Criteria	In item 10, change systolic and diastolic BP position from "supine" to "sitting"	To increase the feasibility at site operation level.

Section # and Name	Description of Change	Brief Rationale
8.2.2 Vital Signs	Change from “supine” to “sitting position”, from “pulse rate” to “heart rate”, and from “axillary” to “tympanic” temperature.	To increase the feasibility at site operation level.
9.3.2.3 Vital signs	Change from “pulse rate, body temperature” to “heart rate, tympanic temperature”,	Ensure consistent with Section 8.2.2
1.3 SoA	In note “f”, changed from “supine” to “sitting position”, from “pulse rate” to “heart rate”, from “body” to “tympanic”. Add “Standing and supine BP will be additionally collected on Day -1”	Ensure consistent with Section 8.2.2. Describe standing and supine BP to be collected for exclusion criteria assessment.
1.3 SoA	Delete “-4 h” in the column of “Pre-dose”	Ensure consistent with Section 8
10.3 Appendix 3: Clinical Laboratory Tests	Delete “The results of each test must be entered into the CRF”. Delete “HTLV-1 antibody” in Table 2.	Results of Screening items are not required to be entered. HTLV-1 antibody is not included in screening tests.
2.2 Background 2.3 Benefit/Risk Assessment and 11. Reference	Change Belimumab IB version to 2011N128591_05, IB Version 15； delete IB supplement number in Section 2.3 and 11.	Update to latest IB version
Title page	Change “China” to “Shanghai” in Sponsor Contact Address	Corrections.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An open-label, randomized, parallel group, single dose study to investigate the PK and safety of belimumab 200 mg intravenous and 200 mg subcutaneous via auto-injector in Chinese healthy participants.

Short Title: Single dose study to investigate the PK and safety of belimumab 200 mg intravenous and 200 mg subcutaneous via auto-injector in Chinese healthy participants.

Rationale:

The purpose of this study is to characterize the pharmacokinetic profile and safety profile of 200 mg single dose of belimumab, administered either intravenously or subcutaneously via auto-injector in Chinese healthy participants. In the global development program, both belimumab intravenous (IV) and belimumab subcutaneous (SC) administration of belimumab have been evaluated. Following the global SC formulation development, this Phase I study in healthy Chinese participants will investigate the safety and PK of belimumab after single dose SC administration of a 200 mg/mL liquid formulation. The dose used in this study is the same as the dose used in the Phase III study (study BEL112341) in the global development of belimumab SC. The same dose, 200 mg, given IV will also be tested to compare the safety and pharmacokinetic profile between the subcutaneous and intravenous administrations. All PK data collected from the study will be combined with other PK data available and analyzed using a population PK (POPPK) model. The POPPK analysis results will be reported separately. The data from this study, and the planned POPPK analysis will be used to support belimumab SC for China regulatory market application in SLE and other autoimmune disease.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To characterize the PK profile of belimumab 200 mg after intravenous and subcutaneous administration via auto-injector in healthy Chinese participants	Individual concentration-time profiles, and median/mean profiles of belimumab by treatment groups.
Secondary	
To evaluate the safety and tolerability of IV and SC administration via auto-injector of belimumab 200 mg in healthy Chinese participants	Safety parameters including vital signs, ECGs, clinical laboratory test, local tolerance evaluation (injection site), and adverse events.

Overall Design:

This is an open-label, randomized, parallel group, single dose study in Chinese healthy participants. Each participant will receive single dose of belimumab administered either intravenously or subcutaneously. Intravenous dose will be administered over approximately 1 hour. The diluted solution volume for IV will be 250 mL in total. The subcutaneous dose will be administered in the thigh via prefilled auto-injector device. The injection may take up to 15 seconds to complete.

Disclosure Statement:

This is parallel group 2 arm, open-label study.

Number of Participants:

Thirty-six participants will be enrolled.

Intervention Groups and Duration:

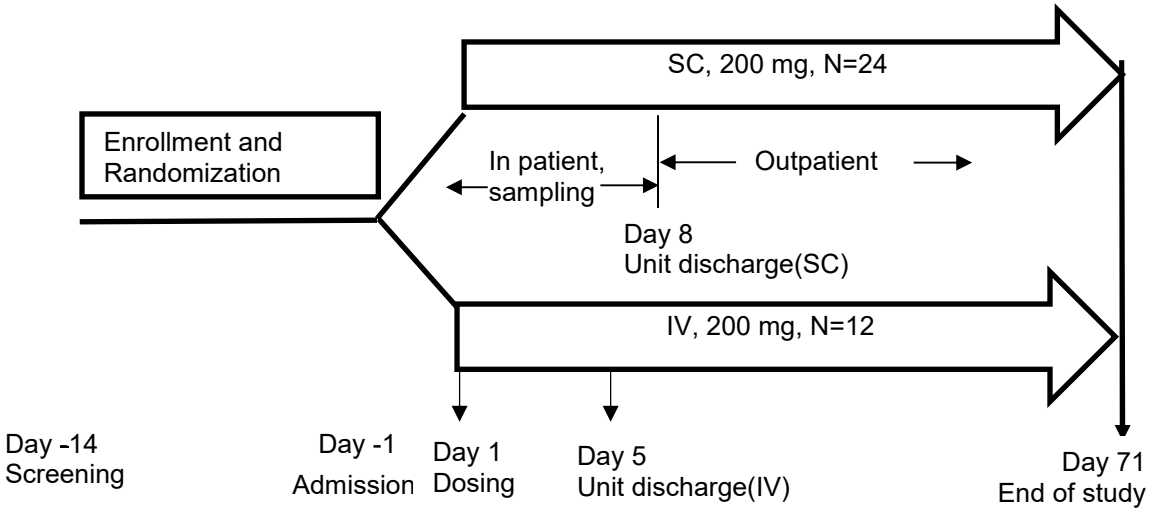
Treatment Groups and Duration: Participants will be assigned to Group A or B as shown in the following table in accordance with the randomization. Randomization will be stratified by body weight (<65 kg and ≥65 kg). In each stratum, the participants will be allocated to the two treatment groups by 1: 2 (IV:SC) ratio.

Group A (N=12)	Group B (N=24)
belimumab 200 mg single IV	belimumab 200 mg single SC

Data Monitoring Committee: No.

1.2. Schema

Figure 1 Study Design



1.3. Schedule of Activities (SoA)

Study Day	**Screening (-14~-1)**	**-1**	**1**									**2**		**3**		**4**	
Hour (Relative to dose completion)			Pre-dose	-1 h	-30 min	0 h	1 h	2 h	4 h	6 h	12 h	24 h	36 h	48 h	60 h	72 h	84h
Informed consent	X																
Outpatient visit	X																
Admission to unit		X															
Demographics and Medical history[a]	X																
Body weight and BMI[b]	X	X															
Height	X																
Inclusion/Exclusion Criteria	X	X	X														
Randomization		X															
Laboratory and Clinical																	
Urine Drug Screen	X																
Alcohol Breath Test		X															
HIV, syphilis, HepB and HepC Screen	X																
Chest X-Ray	X																
QuantiFERON-TB Gold Test	X																
Pregnancy test (female with fertility) [c]	X	X[c]															
12-lead ECG [d]	X																
Hematological/Chemical/Urinalysis tests	X	X[o]															
IgA, IgM and IgG	X																
Physical examination	X	X	X[e]									X[e]		X[e]		X[e]	
Vital signs [f]	X	X	X				X	X	X	X		X	X	X	X	X	X
AE, SAE assessment [g]	←==========→																
Concomitant drug review	←==========→																
Dosing and PK Sampling																	
Study Treatment Dosing IV only				←1 h[h]→													
Study Treatment Dosing SC						X											
PK blood sample IV			X		X[n]	X	X			X		X		X		X	
PK blood sample SC			X							X		X		X		X	
Local tolerance evaluation (SC only) [j]						X[k]	X		X			X[l]		X[l]		X[l]	

Study Day	**5**	**6**	**7**	**8**	**11**[i,m]	**15**[i,m]	**22**[i,m]	**29**[i,m]	**43**[i,m]	**57**[i,m]	**71/Follow-up**[i,m]
Hour (Relative to dose completion)	96 h	120 h	144 h	168 h	240 h	336 h	504 h	672 h	1008 h	1344 h	1680 h
Outpatient visit				X[m]	X[i]	X	X	X	X	X	X
Discharge	X[m]			X[i]							
Laboratory and Clinical											
Pregnancy test (Only for female with fertility) [c]								X		X	X
12-lead ECG[d]											X
Hematological/Chemical/Urinalysis tests				X				X		X	X
IgA, IgM and IgG						X		X		X	X
AE, SAE assessment [g]	←==========										==========→
Concomitant drug review	←==========										==========→
Physical examination	X[e]	X[ie]	X[ie]	X[e]	X[ie]	X[e]	X[e]	X[e]	X[e]	X[e]	X
Vital signs	X	X[i]	X[i]	X	X[i]	X	X	X	X	X	X
PK blood sample IV	X			X		X	X	X	X	X	X
PK blood sample SC	X	X	X	X	X	X	X	X	X	X	X
Local tolerance evaluation (SC only) [j]	X[l]										

a. Medical history includes allergy history, alcohol and smoking history, use of concomitant medication, blood donation history, other clinical trials attendance history, general condition and other which would be assessed as related to the Inclusion/Exclusion Criteria listed in Section 5.1 and Section 5.2.
b. Body weight on day-1 would be used for study stratification.
c. Pregnancy (serum or urine) test is only for female participants with fertility. Urine pregnancy test is required at screening visit, Day 29, Day 57 and Day 71. Serum pregnancy test is required at Day -1. Only conduct serum pregnancy test for subjects screened on Day -1. Pregnancy beyond Day 71 and within 16 weeks will be assessed with a home kit and participants can report the results via phone to site.
d. Single ECG, or triplicate ECGs obtained over a brief recording period.
e. Symptom-driven physical examination.
f. Vital signs include BP (sitting position), heart rate and tympanic temperature. Standing and supine BP will be additionally collected on Day -1.
g. SAE collection will start from inform consent, AE collection will start from study treatment administration. Injection site reactions (e.g., induration, erythema, edema, rash, pruritis, pain) are to be recorded on the AE form of CRF.
h. The IV infusion time will be over and close to 1hour. It's important to record the actual infusion start time and completion time in the medical notes.
i. SC only. The outpatient visits planned for SC is on Day 11,15, 22, 29, 43, 57,71.
j. Local tolerance evaluation: inspection of injection site reactions (e.g., induration, erythema, edema, rash, pruritis, pain) are to be recorded on the AE form of CRF.
k. Immediately after injection completed.
l. Local tolerance evaluation windows on Day 2,3,4,5 are ±4hrs.
m. IV only. The outpatient visits planned for IV is on Day 8,15,22,29,43,57,71.
n. The -30 min PK timepoint is calculated at 30 mins after the start of belimumab IV infusion.

o. Clinical laboratory test results at screening visit will be used for inclusion/exclusion assessment. For subjects who screened on Day-1, only conduct laboratory tests once on the same day.

2. INTRODUCTION

2.1. Study Rationale

Belimumab (belimumab) is a recombinant, human, immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that binds and antagonizes the biological activity of soluble B lymphocyte stimulator (BLyS) protein, a member of the tumor necrosis factor (TNF) ligand superfamily that promotes the survival of B lymphocytes and stimulates the differentiation of B cells into immunoglobulin-producing plasma cells. The biologic profile of belimumab suggests that it may have therapeutic benefit in the treatment of autoimmune diseases where BLyS appears to play a role in disease pathogenesis. In the treatment of systemic lupus erythematosus (SLE), corticosteroids are generally indicated. The initial dose is determined according to the severity of disease. In active cases with severe visceral lesions, coadministration of immunosuppressants is considered. For these treatments, there are concerns about adverse reactions or lack of efficacy in refractory cases. Thus, there is an urgent need for drugs with improved efficacy and safety for the treatment of SLE.

In the global development program, both intravenous (IV) and subcutaneous (SC) administration of belimumab have been evaluated. The first market product was belimumab IV, which was initially approved in the US on 09 March 2011 for the treatment of adult patients who had active, autoantibody-positive SLE and were receiving standard therapy. The approved dosing regimen is 10 mg/kg by intravenous infusion over 1 hour every 2 weeks for 3 doses and then every 4 weeks thereafter. Overall, marketing approval of Benlysta IV has been achieved in over 65 countries by the end of 2016. Following Benlysta IV, Benlysta SC has been approved in US and other countries since 2017.

In the China development program, the clinical trials for Benlysta IV including a completed phase I study (study number 200909_single dose PK study in SLE patients, GlaxoSmithKline Document number 2017N342008_00) and a completed regional phase III study (study number BEL113750_regional study to evaluate the efficacy and safety of belimumab IV 10 mg/kg in subjects with active SLE of Northeast Asia, GlaxoSmithKline Document number, 2014N216965_01). The planned study described in this protocol will assess the safety, pharmacokinetic profile of 200 mg IV and 200 mg SC in Chinese healthy participants. The data of this study will be used to bridge other Benlysta IV and SC clinical data to support the registration of belimumab SC administration in China.

2.2. Background

In vitro and *in vivo* studies of belimumab have demonstrated its ability to bind BLyS and inhibit its activity, while animal models and ex vivo data collected from patients with RA, SLE, Sjogren's Syndrome, ITP and ANCA-associated vasculitis (e.g., Wegner's granulomatosis) suggest that elevated BlyS levels may be associated with the pathogenesis of these autoimmune diseases in which B cells are dysregulated as evidenced by pathogenic autoantibody production [Zhang, 2001; Cheema, 2001; Groom, 2002; Sanders, 2006; Emmerich, 2007; Petri, 2008; Bosello, 2008; Schneeweis, 2010]. In cynomolgus monkeys, belimumab has been shown to significantly reduce B cell

representation in lymphoid tissue after 1 month of treatment and reduce peripheral blood B cells after 3 months of treatment. The ability of belimumab to reduce B cells led may be helpful for the reduction of B lymphocyte activity in patients with autoimmune disease. A detailed description of the chemistry, pharmacology, efficacy, and safety of belimumab is provided in the Investigator Brochure (IB) [GlaxoSmithKline Document number 2011N128591_05, IB Version 15].

2.3. Benefit/Risk Assessment

Belimumab has been generally well tolerated in the clinical trial populations studied.

In a Phase I study (Study BEL114448), including both SC and IV formulations of belimumab in 118 healthy participants, the most frequent AEs were injection site pain, headache, injection site erythema, diarrhea, and pharyngitis. In the SC multiple-dose groups, 2 SAEs were reported. One subject experienced serious appendicitis (possibly related, resolved) on Day 13 (after 2 injections) resulting in discontinuation of study agent and another subject with a history of a torn anterior cruciate ligament and right knee pain reported moderate pain in extremity (not related) that occurred on Day 1. There were no serious or severe injection site reactions reported, and most reports of pain were mild and occurred immediately after the injection. No hypersensitivity reactions or deaths were reported.

In a Phase I SC study (BEL116119, GlaxoSmithKline Document Number 2012N137242_00) including 16 healthy male Japanese subjects who were randomized and treated with a single dose of 200 mg belimumab administered by either IV infusion or SC injection. In total, 7 AEs were observed in 5 subjects. All events were mild or moderate in intensity. Six AEs were reported in 4 subjects in the IV group, and 1 AE was reported in the SC group. No AEs related to injection site reactions were reported during the study. Among 7 AEs, one event (cellulitis) reported in the IV group was judged to be related to the belimumab. No SAEs or deaths were reported during this study. There were no withdrawals, and all 16 subjects completed the study. No clinically significant changes were noted in vital sign, electrocardiogram (ECG) or laboratory test except those judged as AEs.

In Phase III IV study(BEL113750) of the Northeast Asia, the incidences of AEs during the double-blind period in the belimumab group were similar with or lower than those in the placebo group. SAEs were reported overall for 18.3% and 12.3% of participants in the placebo and belimumab 10 mg/kg IV groups, respectively. The SAE with overall highest incidence was infections and infestations (5.5% placebo, 5.3% belimumab). No clinically meaningful differences were observed between treatment groups with regards to the incidence of SAEs. In sub-group analysis of the China cohort, SAEs were reported for 14.4% and 9.0% of subjects in the placebo and belimumab10 mg/kg groups, respectively. In both treatment groups, the incidence of SAEs in the China cohort was lower than the Overall population (18.3% placebo, 12.3% belimumab) and the Not-China cohort (30.9% placebo, 23.8% belimumab). The incidence of SAE in infections and infestations was 5.6% for placebo and 3.6% for belimumab).

Identified risks include hypersensitivity/infusion reactions and infections. Potential risks include malignancies; immunogenicity; effects on immunizations, including interactions with live vaccine; and psychiatric events including depression and suicidality. Malignancy and immunogenicity risks are theoretically associated with long-term use.

Further details about the potential risks and expected benefits of belimumab can be found in the IB [GlaxoSmithKline Document number 2011N128591_05, IB Version 15]

2.3.1. Risk Assessment

Known/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK 1550188]		
Hypersensitivity and Post-Injection and Infusion Reactions	Administration of belimumab may result in infusion and hypersensitivity reactions, which can be severe and can be fatal. Serious infusion and hypersensitivity reactions affected less than 1% of patients and included: anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnoea. Delays in the onset of hypersensitivity reactions have been observed. Infusion reactions following administration of belimumab occurred more frequently on the first 2 infusion days and tended to decrease with subsequent administrations. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema. In the clinical study for BENLYSTA administered subcutaneously, the frequency of injection site reactions was 6.1% (34/556) for patients receiving BENLYSTA plus standard therapy and 2.5% (7/280) for patients receiving placebo plus standard therapy. These injection site reactions (most commonly pain, erythema, hematoma,	Exclusion of participants with a history of atopy or anaphylactic reaction to any food, drug or insect bite/sting or a history of allergic reaction to parenteral administration of contrast agents, foreign proteins, or monoclonal antibodies. Participants will remain under medical supervision in the institute at least up to the 96 hours post dose assessments, which should be long enough to detect early reactions to the study drug. Participants will be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Belimumab will be administered by a healthcare professional prepared to treat hypersensitivity reactions including anaphylaxis. The local injection site reaction will be evaluated for SC group during the study.

Known/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	pruritus, and induration) were mild to moderate in severity. The majority did not necessitate discontinuation of treatment.	
Infections	Infections occurred in a slightly greater proportion of participants treated with belimumab compared with placebo. Infections occurring in at least 3% of patients receiving belimumab and at least 1% more frequently than patients receiving placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis, and gastroenteritis viral. Serious infections occurred in 5% of patients receiving either belimumab or placebo	Exclude participants with a history of any infection requiring hospitalization, antivirals or antibiotics within 4 weeks prior to Day 1., a history of or positive test at screening for HIV, Grade 3 or 4 lymphopenia, Grade 3 or 4 IgG or IgA deficiency. Patients will be excluded for serologic evidence of Hepatitis C (positive test) and evaluated for serologic evidence of Hepatitis B (HB) infection (HbsAg and anti-HbcAb). Patients with a positive HbsAg or a positive anti-HbcAb will be excluded. Monitor patients for signs and symptoms of infection, monitor laboratory values, and request that patients report signs of infection. Treat infections immediately and appropriately. If patient becomes hepatitis B core antibody positive and/or develop an ALT and/or AST >2.5 x ULN, obtain quantitative hepatitis B virus Deoxyribonucleic acid (DNA). If the quantitative hepatitis B virus DNA result shows detectable viral loads, then the participant must be treated immediately and appropriately.

Known/Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Effects on immunizations including reactions with live vaccines	No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving belimumab. 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. Limited data suggest that belimumab does not significantly affect the ability to maintain a protective immune response to immunizations received prior to administration of belimumab.	The study will exclude patients who have received a live vaccine within 30 days of Day 1 or anticipate receipt of a live vaccine during the study. Do not administer live vaccines concurrently.
Malignancies	As with other immunomodulating agents, the mechanism of action of belimumab may increase the potential risk for the development of malignancies.	Exclude patients with a history of malignant neoplasm within the last 5 years, except for adequately treated basal or squamous cell cancers of the skin, or carcinoma in situ of the uterine cervix. Monitor patients for signs and symptoms of malignancy, monitor laboratory values, request that patients report signs and symptoms. Treat appropriately.

2.3.2. Benefit Assessment

Participants enrolled into this study are Chinese healthy participants. The participants' involvement will contribute to the PK and safety profiles of belimumab IV and SC in the Chinese population.

2.3.3. Overall Benefit:Risk Conclusion

This study will be conducted in healthy participants. Risk mitigation measures have been taken to minimise the risk to participants in this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To characterize the PK profile of belimumab 200 mg after intravenous and subcutaneous administration via auto-injector in healthy Chinese participants	Individual concentration-time profiles, and median/mean profiles of belimumab by treatment groups.
Secondary	
To evaluate the safety and tolerability of IV and SC administration via auto-injector of belimumab 200 mg in healthy Chinese participants	Safety parameters including vital signs, ECGs, clinical laboratory test, local tolerance evaluation (injection site), and adverse events.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, randomized, parallel group, single dose study in healthy Chinese participants. Each participant will be randomized at 1:2 ratio to receive one treatment of either IV or SC administration of belimumab 200 mg. The intravenous dose will be administered over approximately 1 hour. The diluted solution volume for IV will be 250 mL in total. The subcutaneous dose will be administered in the front of the thigh via auto-injector device within approximately 15 seconds. The total study duration is approximately 13 weeks.

Protocol waivers or exemptions are not allowed with the exception for immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of activities (SOA) Table Section 1.3, are essential and required for study conduct.

4.2. Scientific Rationale for Study Design

This is an open label study in which belimumab will be administered either intravenously or subcutaneously to each participant. A parallel design is selected as the t1/2 of belimumab is longer than 2 weeks (18-19 days) based on the POPPK analysis, and therefore a washout of at least 10 weeks would have been required for a crossover design.

4.3. Justification for Dose

An international Phase III study (BEL112341, GlaxoSmithKline Document Number, 2014N216963_01) of the SC formulation of belimumab over 52 weeks has been completed in 2016, and the efficacy and safety have been confirmed. belimumab SC was received FDA approval in 2017 to treat adult patients who had active, autoantibody-positive SLE and were receiving standard therapy. China had conducted a regional Phase III study BEL113750 for IV formulation and the data will be used to support the belimumab IV in China Market application. In addition, there is a completed single dose Phase I study 200909 which investigated the safety, tolerability and PK/PD of single dose IV belimumab 10 mg/kg in Chinese participants with SLE.

Following a single SC administration of the 200 mg/mL solution belimumab product in healthy non-Chinese participants (study BEL114448), the absolute bioavailability of belimumab ranged from 72%-76%. As expected, IV dosing results in higher steady-state Cmax and lower steady-state Cmin than SC dosing.

Following the global SC formulation development, this Phase I study in healthy Chinese participants will investigate the safety and PK of belimumab after single dose SC administration of a 200 mg/mL liquid formulation. The dose used in this study is the same as that used in the Phase III study in the global development of SC belimumab. The 200 mg IV dose will also be tested to compare the safety and pharmacokinetic profiles between the SC and IV administrations. There are observed differences between Chinese and western populations related to e.g. body weight in that exposure in Chinese subjects are on average higher, but the difference is clinically insignificant because of the safety profiles of belimumab (up to 20 mg/kg IV and 240 mg SC dose regimens were tested in previous studies). The distribution of individual steady-state average concentration (Cavg_ss) observed following 10 mg/kg IV dosing every 4 weeks and those estimated from 200 mg SC weekly dosing (from post-hoc of POPPK analysis, based on data from study C1056, C1057 and BEL113750) are largely overlapping, supporting the potential efficacy of the SC 200 mg QW dosing. Therefore, the two dosing regimens of IV 10 mg/kg Q4W and 200 mg QW chosen for this PK study is considered reasonable.

The data from this study will be used to support belimumab SC in China regulatory application including SLE and other autoimmune disease.

4.4. End of Study Definition

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

The end of the study is defined as the last participant's last visit.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Informed Consent

1. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Age

2. Chinese healthy male or female between 18 and 45 years of age inclusive, at the time of signing the informed consent.

Type of Participant

3. Healthy as defined as being free from clinically significant illness or disease as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, vital sign, laboratory tests and ECG. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied, may be included only if the investigator (in consultation with the GSK medical monitor if necessary) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

4. Non-smoker or ex-smoker having ceased smoking for at least 6 months

Weight

5. Body weight ≥45.0 kg for females, ≥50.0 kg for males, and BMI (body mass index) within the range 19.0≤-≤26.0kg/m^2.

Sex

6. Both male and female subjects are eligible to participate.

   A female participant is eligible to participate if she is not pregnant (see Appendix 2), not breastfeeding, and at least one of the following conditions applies:

   i. Not a woman of childbearing potential (WOCBP) as defined in Appendix 2

   OR

   ii. A WOCBP who agrees to follow the contraceptive guidance in Appendix 2 during the treatment period and for at least 16 weeks after the last dose of belimumab.

5.2. Exclusion Criteria

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

Laboratory Assessment

1. A positive test for syphilis, positive Hepatitis C antibody, HIV antigen /antibody, at screening. For Hepatitis B: participants with a positive HbsAg and/or a positive anti-HBc result will be excluded.

2. A positive result of pre-study drug screen (including at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).
3. Alanine transaminase (ALT) or Alanine phosphatase(AST)>1.2x upper limit of normal (ULN).

4. Bilirubin >1.2xULN (isolated bilirubin >1.2xULN is acceptable if bilirubin is fractionated and **direct** bilirubin <35%).

5. QTc >450 msec based on single ECG.

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

6. Immunoglobulin (M, A, G) level is < Lower limit of normal (LLN) at screening.

Medical Conditions

7. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

8. History of major organ transplant: e.g., heart, lung, kidney, liver, or hematopoietic stem cell transplant.

9. History of malignant neoplasm within the last 5 years, except for adequately treated basal or squamous cell cancers of the skin, or carcinoma in situ of the uterine cervix.

10. Participants with a sitting position systolic blood pressure <90 mmHg or ≥140 mmHg and/or a sitting diastolic blood pressure <50 mmHg or ≥90 mmHg and/or systolic blood pressure drop from supine to standing of >30 mmHg.
11. Symptomatic herpes zoster within 3 months prior to screening.

12. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, chest X-rays (posteroanterior) and a positive (not indeterminate) QuantiFERON-TB Gold test.

    NOTE: The use of QuantiFERON-TB Gold test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression.

13. History of any infection requiring hospitalization or treatment with antivirals, antibiotics, anti-fungals, anti-parasitic agents or vaccination within 30 days prior to the administration of study medication.

14. History of regular alcohol consumption exceeding, on an average, 14 drinks/week for men or 7 drinks/week for female (1 drink = 5 ounces [150 mL] of wine or 350 mL of beer or 1.5 ounces [45 mL] of 80 proof distilled spirits) within 6 months of screening.

Prior/Concurrent Clinical Study Experience

15. The participant had participated in a clinical study or post-marketing study with an investigational or a non-investigational product during the previous 4 months or 5 half-lives (whichever is longer) preceding the administration of study medication of this study.
16. Exposure to more than 4 new chemical entities within 12 months prior to the dosing day.

17. The participant planned to concurrently participate in another clinical study or post-marketing study.

Prior/Concomitant Therapy

18. Use of any prescription or non-prescription medications including vitamins, herbal and dietary supplements within the 14 days or 5 half-lives (whichever is longer) prior to the administration of study medication.
19. History of B cell targeted therapy (rituximab, other anti-CD20agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], BlyS-receptor fusion protein [BR3], TACI-Fc, LY2127399 [anti-BAFF] or belimumab) at any time.

20. Have received a live vaccine within 30 days of Day 1 or anticipate receipt of a live vaccine during the study or within 120 days after the last dose administration of study drug.

Other Exclusions

21. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy (excluding pollen allergy) without current symptoms.

22. History of anaphylactic reaction to any food, drug, or insect bite/sting.

23. History of allergic reaction to parenteral administration of contrast agents, foreign proteins, or monoclonal antibodies.

24. Donation of blood or blood products or significant blood loss in excess of 400 ml within 4 months or 200 ml within 2 months prior to administration

25. Participant is mentally or legally incapacitated, or unwillingness or inability (including mentally or legally incapacity) to follow the procedures outlined in the protocol.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Each participant must visit the medical institution at Day -1, 8 (IV group only), 29, 57 and 71 in a fasted state for clinical laboratory tests.

5.3.2. Alcohol, and Tobacco

- Participants will abstain from ingesting alcohol for 24 hours before the start of dosing until final follow-up examination.
- Use of tobacco products is not allowed from the time a participant gives consent to participate in the study until after the final follow-up visit.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.3.4. Other restrictions

- Participants must refrain from taking any other medication (prescription, nonprescription, herbal and dietary supplements) from administration of study medication until the study period, with the exception for medication for treatment of adverse event permitted by investigator/sub-investigator.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized 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 Study Intervention includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs). Laboratory retest is allowed if required or if investigator judged any error in lab result.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION(S)

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

6.1. Study Intervention(s) Administered

	Study Intervention	
Product name:	Belimumab 400 mg vial for IV	Belimumab 200 mg/mL auto-injector for SC
Formulation description:	Belimumab 400 mg per vial plus excipients (Citric acid monohydrate / Sodium citrate dehydrate / Sucrose / Polysorbate 80)	200 mg/mL belimumab in 0.65 mg/mL L-histidine, 1.2 mg/mL L-histidine monohydrochloride, 6.7 mg/mL sodium chloride, 5.3 mg/mL L-arginine hydrochloride, 0.1 mg/mL polysorbate 80, with pH 6.0.
Dosage form:	Lyophilized cake for reconstitution and dilution in normal saline	Sterile, liquid product
Unit dose strength(s)/Dosage level(s):	400 mg per vial (to contain 80 mg/mL when reconstituted with 4.8 mL sterile water for injection [SWFI]) /200 mg per dose	200 mg/mL; 1 mL (deliverable)
Route/ Administration/ Duration	Intravenous / Single dose	SC injection/single dose
Dosing instructions:	Should be infused approximately over 1 hr	Single dose in the front of the thigh
Physical description:	White to off-white cake in a 20 mL vial	Clear to opalescent, colorless to pale yellow sterile solution sterile solution for SC injection in a single-use, prefilled syringe contained within an auto-injector device
Manufacturer/source of procurement:	Drug substance: manufactured by GSK GMS BIOPHARM US (Rockville). Drug Product: manufactured by GSK Parma, Italy.	The auto-injector components are manufactured by Scandanavian Health Limited (SHL) and assembled with the prefilled syringe at GSK, Barnard Castle, UK

	Study Intervention	
Method for individualizing dosage:	Solution volume will be adjusted by a pharmacist in the institute (Calculated dose is diluted into a normal saline IV bag for infusion)	No adjustment
Device	Intravenous cannula and infusion equipment (provided by clinical site)	Auto-injector

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 is injection device the auto-injector.
- The auto-injector components are manufactured by Scandanavian Health Limited (SHL). The auto-injector components are assembled with the prefilled syringe at GSK Barnard Castle.
- Instructions for use of these injection devices are provided in the Study Reference Manual (SRM).
- 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 8.3.6).

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff administer study treatment. All study treatments 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. Study treatment is to be stored at 2-8°C (refrigerator) /protected from direct sunlight/etc. Maintenance of a temperature log (manual or automated) is required.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The investigator or the head of the medical institution, or designated site staff (IP storage manager) must maintain study treatment accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to GSK and the amount administered to Participants. The required accountability unit for this study will be vial/syringe. Discrepancies are to be reconciled or resolved.

4. A description of the methods and materials required for reconstitution of solution for IV dose are provided in the SRM.
5. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
6. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
7. Precaution will be taken to avoid direct contact with the study treatment. A 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. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the GSK medical monitor of any unintentional occupational exposure.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a randomized open-label study. A randomization schedule will be generated prior to the study by the study statistician, using an internal validated software (i.e. RandAll NG). Participants will be randomly assigned to either IV group or SC group at 1:2 ratio. The randomization is stratified by body weight (<65 kg and ≥65kg).

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with the:

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

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

6.5.1. Permitted Medications

Concomitant medications and non-drug therapy other than the investigational drug will not be permitted from 14 days or 5 half-lives before the first dose to the completion of the post-study screen (or additional/follow-up examination) other than at the discretion of the

investigator/sub investigator for instances of emergency treatment (Exclusion Criteria Section 5.2).

6.5.2. Prohibited Medications and Non-Drug Therapies

Live vaccine is not allowed during the study.

6.6. Dose Modification

There is no specific adjustment / stopping criteria for the study. Each participant will receive a single dose, either intravenously or subcutaneously in the study.

6.7. Intervention after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because only healthy participants are eligible for study participation.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not GSK is providing specific post-study treatment.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

7.1.1. Liver Chemistry Stopping Criteria

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

These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 5.

7.1.2. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
    - For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
    - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data*

being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.

- The QTc should be based on the average of triplicate ECG readings obtained over a brief (e.g., 5-10 minute) recording period.

A participant that meets the criteria below will be withdrawn from the study intervention.

- QTcB or QTcF >500 msec

Withdrawal decisions are to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates prolonged QTc interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the participant should be discontinued from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

If participants who completed dosing of study medication meet the stopping criteria, they may continue safety monitoring and PK blood sampling as described in SoA, at the discretion of the investigators.

7.1.3. Temporary Discontinuation

If a participant does not complete the dose of investigational product(s), the participant will be considered to have prematurely discontinued investigational product(s). The investigator must make every effort to perform the follow up assessments.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety behavioural, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- If a participantwithdraws or is withdrawn from the study, all assessments scheduled for the final visit should be completed, if the participant consents to this being done.

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.
- Detailed procedures for obtaining each assessment are provided in the SRM.
- For the IV group, the end time of the infusion will be designated as Time 0. Both the start time and the end time of infusion should be documented in the source document.
- Whenever two or more examinations are scheduled for the same nominal time, the timing of the assessments should allow the blood draw for PK analysis to occur at the exact nominal time. It's essential that the exact time of blood sampling, however, should still be accurately recorded.
- Time assessment window of each examination is as follows:

Study Day	Hrs relative to dose	Safety examinations [a]	Blood sampling for PK
Day-1	Previous day	-24 hrs	Any time
Day 1	Pre-dose	Any time before dosing	Any time before dosing
Day 1	30 mins after the start of IV	NA	±5min
Day 1	0 h	For local tolerance evaluation, conduct immediately after SC injection[c]	+5min [b]
Day 1	1hrs after dose completion	±10 min	±5 min
Day 1	2-4 hrs after dose completion	±15 min	±5min
Day 1	6 hrs after dose completion	±30 min	±10 min
Day 1-2	12-24 hrs after dose completion	±1 h	±15 min
Day 2-7	36-144 hrs after dose completion	±2 h	±30 min

Study Day	Hrs relative to dose	Safety examinations [a]	Blood sampling for PK
Day 8-15	168-336 hrs after dose completion	± 1day [b] ±4 h [c]	± 1day [b] ±4 h [c]
Day 22-57	504-1344 hrs after dose completion	±1 day	±1 day
Day 71	1680 hrs after dose completion	±2 days	±2 days

a. Including physical examinations, vistal signs, local tolerance, ECG, clinical safety laboratory assessments and other applicable tests
b. IV group
c. SC group

- 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 treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The following demographic parameters will be captured: date of birth, gender, race and ethnicity. Medical/medication/alcohol history, allergy to any drug, use of concomitant medication, blood donation, participation in clinical trials during the past 4 months, smoking, presence of participant's general practitioner, general condition, food habit will be assessed as related to the eligibility criteria listed in Section 5.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded at screening visit and/or day-1 per SoA.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Systolic and diastolic blood pressure (sitting position), heart rate, and tympanic temperature will be measured. Timepoints of measurements of vital signs are specified in the SoA(see Section 1.3). At the discretion of the Investigator, vital signs may be assessed at unscheduled visits.

8.2.3. Local tolerance evaluation

- On Day 1, inspection of injection site reactions (e.g., induration, erythema, edema, rash, pruritis, pain) will be assessed and recorded. All measurement timings are detailed in the SoA (Section 1.3) and further details is in SRM.

8.2.4. Electrocardiograms

- A Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

8.2.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA 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 71 days after the last dose of study treatment 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 3, must be conducted in accordance with the laboratory manual and the SoA.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

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

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of study treatment until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 4. 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 in former study participants. 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 treatment or study participation, the investigator must promptly notify the sponsor.

8.3.2. 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 4.
- 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.

8.3.3. 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, AEs 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 4.

8.3.4. 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.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 16 weeks following last dose.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy. Pregnancy beyond Day 71 and within 16 weeks will be assessed with a home kit and participants can report the results via phone to site. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

  Any SAE occurring in association with a pregnancy, brought to the investigator's (or sub-investigator's) attention after the participant has completed the study and considered by the investigator (or sub-investigator) as possibly related to the IP, must be promptly reported to GSK.

  If a participant has a positive pregnancy test during study participation, complete a Pregnancy Notification Form and fax it to GSK. Follow the participant to determine the outcome of the pregnancy and forward the outcome information using a

Pregnancy Follow-up Form to GSK no later than 6 to 8 weeks following the estimated delivery date.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3.6. Medical Device Incidents (Including Malfunctions)

Medical device (Auto-injector) is being provided for use in this study. In order to fulfil 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 8.3.3 and Appendix 4 of the protocol.

8.3.6.1. 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.

8.3.6.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3). 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.

8.3.6.3. 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 will be sent to the sponsor by electronic data collection tool. If electronic system is unavailable for greater

than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE contactor.

- The same individual will be the contact for the receipt of medical device reports and SAE.

8.3.6.4. 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.

8.4. Treatment of Overdose

For this study, any dose of belimumab >200 mg within a 24-hour time period will be considered an overdose. GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities-until belimumab can no longer be detected systemically (at least 71 days).
3. Obtain a serum sample for PK analysis within 71 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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.

8.5. Pharmacokinetics

Whole blood samples will be collected for measurement of serum concentrations of belimumab as specified in the SoA. 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. Briefly, PK samples from approximately 24 subjects in belimumab SC group will be collected at pre-dose , 6 h, 24 h, 48 h, 72 h, 96 h, 120 h, 144 h, 168 h, 240 h, 336 h, 504 h, 672 h, 1008 h, 1344 h, and 1680 h. In belimumab IV group, PK samples from approximately 12 subjects will be collected at pre-dose , -30 mins (after the start of belimumab IV infusion), 0 h (end of infusion), 1 h, 6 h, 24 h, 48 h, 72 h, 96 h, 168 h, 336 h, 504 h, 672 h, 1008 h, 1344 h, and 1680 h.

Samples will be used to evaluate the PK of belimumab. Each serum sample will be divided into 2 aliquots (1 each for PK and a back-up). Samples collected for analyses of belimumab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

Non-compartmental PK analysis will not be performed for this study.

8.5.1. Sample Analysis

PK sample would be sent to a local bioanalytical laboratory (Covance Laboratories Inc.) and analysed using a validated method (details provided in the SRM).

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Serum immunoglobin (IgG, IgA and IgM) analysis will be conducted per SoA.

Since none of the SLE patients dosed with belimumab 200 mg SC tested positive for anti-belimumab antibodies in the double-blind phase of Study BEL11234, and immunogenicity risks are theoretically associated with long-term use, immunogenicity analysis will not be investigated in this study.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

9.1.1. Sample Size Assumptions

The primary objective of this study is to characterize the PK profile of belimumab 200 mg after intravenous and subcutaneous administration in health Chinese participants. There are no formal hypothesis to be tested and no power calculation performed. The sample size is determined based on following considerations, first to meet the sample size of 20 requirement per Chinese regulatory guidance [China FDA, 2005] for new chemical

entity, therefore, it is aimed to evaluate 20 subjects in SC group. In addition, considering a lower variability observed for IV group in the previous studies, the sample size for IV group is adjusted as 10 participants. In Japan PK study BEL116119 with similar design, the observed Coefficient of variance (CV)% of Cmax in IV group was 17.0%, which was lower than the data in SC group (32.7%). Considering the observed CV% in this PK study would probably be similar with it in BEL116119, the estimated 95% conference interval will be within 17% of point estimation of Cmax for SC group, and within 13% for IV group.
The sample size is further increased to 36 assuming a drop-out rate of 20%. At least 36 participants (30 evaluable participants) will be enrolled into the study and assigned to SC arm and IV arm at 2:1 ratio under each weight stratification category to obtain approximately 20 and 10 evaluable participants in SC and IV treatment arm, respectively.

9.1.2. Sample Size Sensitivity

The above sample size is chosen to meet regulatory requirement for PK studies. No sample size sensitivity analysis will be performed.

9.1.3. Sample Size Re-estimation

No sample size re-estimation will be performed

9.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
Pharmacokinetic Population	The PK Population will include all participants in the Safety population for whom at least one evaluable PK sample will be obtained and analysed.

9.3. Statistical Analyses

9.3.1. Pharmacokinetic Analyses

Serum concentrations of belimumab will be listed and summary statistics, including mean, median, standard deviations per GSK IDSL standard, will be calculated by treatment group and nominal time. Individual concentration-time profiles and median/mean profiles by treatment group will be plotted on both a linear and semilog scale. PK analysis, e.g. non-compartmental analysis, will not be performed for this study alone. All PK data collected from the study will be combined with other PK data available and analyzed using a population PK (POPPK) model. The POPPK analysis results will be reported separately.

9.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.3.2.1. Adverse events

Adverse Events will be coded using MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT). The number and percentage of participants with any adverse events occurring on or after the treatment start date will be summarized by treatment group. The listing of all adverse events will be prepared. The adverse events related to injection site reactions will be identified on the listing.

When adverse events leading to discontinuation, fatal or non-fatal serious adverse events, or other significant adverse events are observed, a listing will be prepared separately.

9.3.2.2. Clinical laboratory evaluation

For clinical laboratory data, summary statistics will be calculated by treatment group and all observed values will be listed. The change from baseline for each parameter will be also summarized.

9.3.2.3. Vital signs

For systolic and diastolic blood pressure, heart rate, tympanic temperature and body weight, summary statistics will be calculated by treatment group and all observed values will be listed. The change from baseline for each variable will be also summarized.

9.3.2.4. 12-lead ECG

The ECG findings will be summarized by treatment group and the listing of ECG findings will be prepared. For 12-lead ECG parameters, HR, PR, QRS, QT and QTc, summary statistics will be calculated by treatment group and all observed values will be listed. The change from baseline for each parameter will be also summarized.

9.3.3. Interim Analyses

No interim analysis is planned in the study.

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 or 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 was enrolled in 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.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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. Committees Structure

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 subjects, 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 participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

10.1.7. 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 SRM

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

10.1.10. Publication Policy

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

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

10.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

   Note: Documentation can come from the site personnel's review of 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-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.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 1.

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive[a] Methods 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[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence 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 drug. 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.

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the standard of care medications, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 16 weeks after the last dose of belimumab. If stricter female or male contraception requirements are specified in the country-specific label for induction and/or maintenance standard of care medications, they must be followed.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.

- Additional pregnancy testing during the treatment period per the SoA and at 16 weeks after the last dose of belimumab as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing using a serum sample, with a sensitivity of 5 mIU/mL will be performed and assayed at Day -1. Urine pregnancy test will be conducted for all other scheduled pregnancy tests and in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- 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 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 treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating will discontinue study treatment or be withdrawn from the study. Participants who discontinue study treatment should be encouraged to continue to participate in study visits in accordance with the SoA (Section 1.3), especially all remaining safety evaluations.

10.3. Appendix 3: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the local 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.

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit			WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Phosphorus
	Gamma glutamyltransferase (GGT)	Uric acid	CK(CPK)	TG
	Amylase	LDH	Albumin	Chloride
	Total cholesterol	HDL Cholesterol	LDL cholesterol	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, occult blood and ketones by dipstick			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Urine drug screen[3]（ to include at minimum: amphetamines, barbiturates,			

Laboratory Assessments	Parameters
	cocaine, opiates, cannabinoids and benzodiazepines） • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • Immunology[3]: HIV antibody, hepatitis B surface antigen [HbsAg], anti-hepatitis B core antibody[HbcAb] and hepatitis C virus antibody, Syphilis • IgA, IgM and IgG • Alcohol breath test[3]

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 and Appendix 4. 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. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. Screening and day -1.

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New 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.

Events NOT 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.

10.4.2. 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 judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may

not be immediately life-threatening or result in death or 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.

10.4.3. 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.
- 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.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a 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.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.4.4. Reporting of SAE to GSK

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

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

Phase I 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≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</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>• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis when investigators consider appropriate
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• 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
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle</td></tr>
</table>

Liver Chemistry Stopping Criteria	
• Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	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]. • 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 treatment 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, 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); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

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 6.1.1 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 labelling 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: Abbreviations and Trademarks

ABBREVIATIONS

Ae	Urinary recovery of unchanged drug
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
BA	Bioavailability
BlyS	B lymphocyte Stimulator
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence Interval
Cmax	Maximum observed concentration
CPK	Creatine phosphokinase
CRF	Case Report Form
CV	Coefficient of variance
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HbsAg	Hepatitis B surface antigen
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical
IDSL	Integrated Data Standards Library
Ig	Immunoglobulin
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
Kg	Kilogram
L	Liter
ln	Naperian (natural) logarithm
LLN	Lower limit of normal
MCV	Mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MRT	Mean residence time
msec	Milliseconds
PD	Pharmacodynamic
PK	Pharmacokinetic
POPPK	Population Pharmacokinetics
QC	Quality control
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
SAE	Serious adverse event(s)
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SOP	Standard Operating Procedure
SLE	Systemic lupus erythematosus
SRM	Study Reference Manual
T	Injection duration
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
UK	United Kingdom
US	United States
WBC	White blood cells

Trademark Information

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