Clinical Study Protocol

Primary Study Intervention(s)	Depemokimab
Other Study Intervention(s)	NA
Study Identifier	214099
Approval Date	16 Mar 2023
Title	An Open-Label, Randomized, Single-Dose, Multicenter, Parallel-Group Study to Compare the Pharmacokinetics of Subcutaneous Depemokimab When Delivered with a Safety Syringe Device or an Autoinjector in Healthy Adult Participants
Compound Number/Name	GSK3511294
Brief Title	Phase 1, Single-Dose Study to Compare the Pharmacokinetics of Depemokimab When Delivered with a Safety Syringe Device or an Autoinjector in Healthy Adult Participants
Sponsor	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor signatory	Jeff Min, MD MSCE Clinical Development Director Clinical Sciences Respiratory

Medical monitor name and contact can be found in local study contact information document

Protocol/Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express physical informed consent of the participant and/or the participant's LAR.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment.
- To co-operate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

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Investigator name	_____
Signature	_____
Date of signature (DD Month YYYY)	_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	16 Mar 2023
Original Protocol	19 September 2022

Amendment 1 (16 March 2023)

Overall rationale for the current Amendment: Important updates, together with a brief rationale, are summarized in the table below.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
1.3: Schedule of activities	Assessment of complement (C3 and C4) timepoints clarified (pre-dose, Week 12, and Week 26)	Clarification
1.3: Schedule of activities and 8.3.1. Physical Examinations	Symptom-directed physical examination clarified as 'brief physical examination' and also 'Injection site evaluation' timepoints separated in Schedule of activities (SoA) for clarity	Clarification
1.3: Schedule of activities and 8.3.2: Vital Signs	Footnote 'g' along with text in aligned section, updated to clarfiy 'respiratory rate' as 1 of the assessment to be performed under 'vital sign examinations	Clarification
1.3: Schedule of activities, 8.3.5: Pregnancy Testing and Appendix 2: Clinical laboratory tests	Footnote 'i' along with text in aligned section updated to clarify '"For the last follow-up visit (W30/D211), Woman of Childbearing Potential (WOCBP) will perform this visit in clinic and a highly sensitive urine pregnancy test will be performed. Male and non-WOCBP participants will complete the visit remotely via phone assessment." Also, footnote "p" clarified to included 'For WOCBP, follow-up visit will be conducted in clinic so that a pregnancy test result can also be collected'	Clarification
5.2.1. Medical Conditions	Exclusion criteria was updated to the clarify the time of conduct of covid-19 screening	Clarification
7.3. Participant discontinuation/withdrawal from the study	The list of 'primary reasons for participant discontinuation/ withdrawal from the study' was updated in alignement with the latest template	Clarification
8: Study Assessments And Procedures	Total blood volume to be requried for assessment updated to '300 mL'	Amendment to increase blood volume drawn for study procedures and

Section # and title	Description of change	Brief rationale
		assessments following CRO required volumes
8.3.1 Physical Examination	Removed the statement “Height and weight will also be measured and recorded”, as it is clarified in SoA.	Clarification
9.4. Interim Analysis	Interim analysis section updated to clarify that the ‘Available PK concentration data from completed participants may be inspected to support development of depemokimab PK model. No changes to the conduct of the study will be implemented as a result of these analyses’’	Clarification
Throughout the document	Formatting (hyperlink update) and consistency changes in alignment with latest protocol template	Administrative change

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

%AUCex	Percentage of AUC(0-inf) due to extrapolation from Tlast to infinity
ADA	Antidrug antibody
ADE	Adverse device effect
ADL	Activities of daily living
AE	Adverse event
AIH	Autoimmune hepatitis
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
AST	aspartate aminotransferase
AUC(0-inf)	Area under the concentration-time curve from time zero extrapolated to infinity
AUC(0-t)	Area under the concentration-time curve from time zero to time of last observed quantifiable concentration
AxMP	Auxiliary medicinal product
BIB	Bioanalysis, Immunogenicity, & Biomarkers
CI	Confidence interval
CL/F	Apparent clearance following extravascular administration
Cmax	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CRF	Case report form
CV	Coefficient of variation
CV_b	Between subject variability
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EDTA	Disodium edetate
FSH	Follicle-stimulating hormone
FTIH	First Time in Human
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HRT	Hormone replacement therapy
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroid

IDFU	Investigational Directions for Use
IEC	Independent Ethics Committee
IFU	Instructions for use
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LABA	Long-acting beta antagonist
λz	Terminal elimination rate constant
mAb	Monoclonal antibody
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
MPO	Myeloperoxidase
Nab	neutralizing antibody
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID/FAAN	Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR3	Proteinase 3
QTcF	QT interval corrected by Fridericia's formula
QTL	Quality tolerance limit
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of Activities
SOC	System organ class
SRM	Study Reference Manual
SSD	Safety Syringe Device
t1/2	Terminal elimination half-life
Tlast	Time of last measurable plasma concentrations
Tmax	Time to maximum observed plasma concentration
ULN	Upper limit of normal
USADE/UADE	Unanticipated serious adverse device event

Vd/F	Apparent volume of distribution following extravascular administration
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential

Trademark Information

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Term	Definition
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational medicinal product	An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a

Term	Definition
	marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
NIMP/ AxMP	A NIMP or AxMP is a medicinal product that is not classified as an IMP in a study, but may be taken by participants during the study, e.g., concomitant or rescue/escape medication used for preventive, diagnostic, or therapeutic reasons or medication given to ensure that adequate medical care is provided for the participant during a study.
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject.
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers

Term	Definition
	to the date on which data collection is completed for all the primary outcome measures.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

An Open-Label, Randomized, Single-Dose, Multicenter, Parallel-Group Study to Compare the Pharmacokinetics of Subcutaneous Depemokimab When Delivered with a Safety Syringe Device or an Autoinjector in Healthy Adult Participants.

Brief Title:

Phase 1, Single-Dose Study to Compare the Pharmacokinetics of Depemokimab When Delivered with a Safety Syringe Device or an Autoinjector in Healthy Adult Participants

Rationale: Refer to Section 2.1.

Objectives, Endpoints, and Estimands: Refer to Section 3.

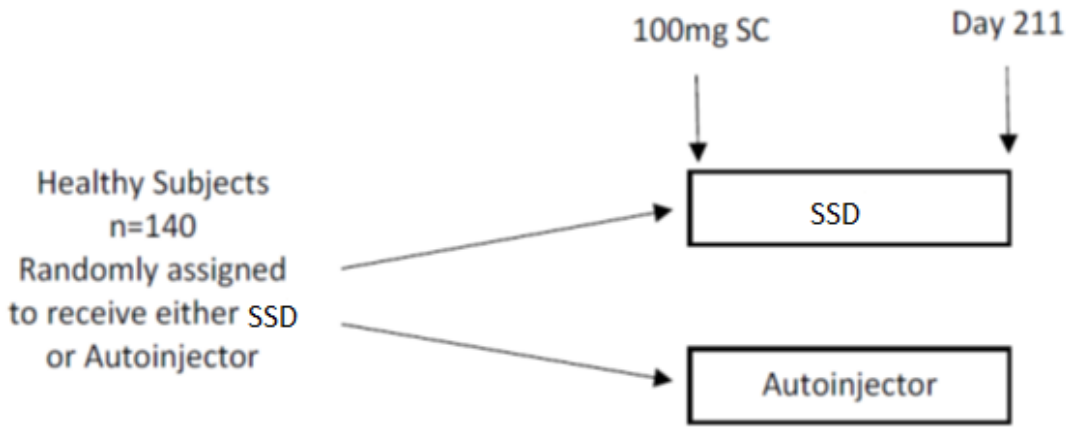
Overall Design: Refer to Section 4.1.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.5.

1.2. Schema

Figure 1 Study design overview



Abbreviation: SSD = Safety Syringe Device

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities.

Procedure[a] (Windows for days and times of procedures are provided in the footnotes)	**Screening**[b]	**In-Patient Period**							**Clinic Visits**									
		Day –1	**Day 1**				**D2**	**D3**	**D5**	**W1**	**W2**	**W4**	**W8**	**W12**	**W18**	**W24**	**Exit Visit/ Early D/C (W26)**	**Last Follow-up Visit**[q] **(W30)**
										D8	**D15**	**D29**	**D57**	**D85**	**D127**	**D169**	**D183**	**D211**
			Pre-dose	**0h**	**2h**	**8h**	**24h**	**48h**	**96h**									
Informed consent	X																	
Inclusion and exclusion criteria	X	X																
Demography	X																	
Medical history[c]	X																	
HIV, Hepatitis B and C screen	X																	
Urine drug screen	X	X																
FSH[d]	X																	
Alcohol test	X	X																
Height, weight, and BMI[e]	X	X															X	
Full physical examination	X																X	
Brief physical examination		X			X			X		X			X					
Injection site evaluation					X			X										
12-lead ECG[f]	X		X				X	X		X	X			X			X	
Vital signs[g]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure[a] (Windows for days and times of procedures are provided in the footnotes)	**Screening**[b]	**In-Patient Period**							**Clinic Visits**									
		Day –1	**Day 1**				**D2**	**D3**	**D5**	**W1**	**W2**	**W4**	**W8**	**W12**	**W18**	**W24**	**Exit Visit/ Early D/C (W26)**	**Last Follow-up Visit**[q] **(W30)**
										D8	**D15**	**D29**	**D57**	**D85**	**D127**	**D169**	**D183**	**D211**
			Pre-dose	**0h**	**2h**	**8h**	**24h**	**48h**	**96h**									
Clinical chemistry (including liver chemistry), urinalysis	X	X								X		X	X	X		X	X	
Complement (C3 and C4)			X											X			X	
Hematology (including blood eosinophil count)	X	X								X		X	X	X		X	X	
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody[h]			X															
Pregnancy test (WOCBP only)[i]	X	X								X	X	X	X	X	X	X	X	X
Parasite screening[j]	X																	
COVID-19 screening[k]		X																
PK blood samples[l]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity blood samples			X									X	X	X			X	
Concomitant medication	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
AE/SAE review	X[m]	X[m]	X[m]	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Device deficiencies (refer to Section 8.4.7)				X														
Admission to clinic[n]		X																
Randomization				X														

Procedure[a] (Windows for days and times of procedures are provided in the footnotes)	**Screening**[b]	**In-Patient Period**							**Clinic Visits**									
		Day –1	**Day 1**				**D2**	**D3**	**D5**	**W1**	**W2**	**W4**	**W8**	**W12**	**W18**	**W24**	**Exit Visit/ Early D/C (W26)**	**Last Follow-up Visit**[q] **(W30)**
										D8	**D15**	**D29**	**D57**	**D85**	**D127**	**D169**	**D183**	**D211**
			Pre-dose	**0h**	**2h**	**8h**	**24h**	**48h**	**96h**									
Study intervention				X														
Clinic visit[o]									X	X	X	X	X	X	X	X	X	
Follow-up																		X[q]

AE = adverse event; ANA = antinuclear antibodies; BMI = body mass index; D = day; D/C = discontinuation; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; FSH = follicle-stimulating hormone; h = hour(s); HIV = human immunodeficiency virus; MPO = myeloperoxidase; PK = pharmacokinetic; PR3 = proteinase 3; SAE = serious adverse event; W = Week; WOCBP = woman of childbearing potential

Notes:

a. When safety and/or PK assessments are collected at the same time point, ECGs, vital signs, and PK blood collections should be performed in the listed order.

b. Screening can be performed up to 30 days before admission to the clinic. Screening procedures may be done at 1 or more outpatient visits, within the screening window. When screening is performed within 3 days of Day -1, blood and urine testing, other than pregnancy testing, does not need to be repeated.

c. Includes history of cardiovascular disease, allergy history, and alcohol use.

d. If required to confirm postmenopausal status.

e. Height will be measured at screening; weight only will be measured study exit/early termination.

f. All 12-lead ECGs will be performed with the participant in a semi-supine position after resting for at least 10 minutes. Pre-dose ECGs will be performed in triplicate to establish the participant's baseline, and post-dose ECGs will be performed as single ECGs. "Pre-dose" triplicate measurement applies only to D1 prior to the dosing (see Section 8.3.3).

g. Vital Signs include assessment of temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate. Blood pressure and heart rate will be measured in triplicate before dosing; single measurements will be taken after dosing. Single temperature and respiratory rate measurements will be taken at all time points. "Pre-dose" measurement applies only to D1 prior to the dosing.

h. A baseline sample will be collected and stored and may be tested if necessary (see Section 7.1.3).

i. For WOCBP, a serum pregnancy test will be done at screening and study exit/early termination. A highly sensitive urine pregnancy test will be done at all other time points. For the last follow-up visit (W30/D211), WOCBP will perform this visit in clinic and a highly sensitive urine pregnancy test will be performed. Male and non-WOCBP participants will complete the visit remotely via phone assessment

j. Only required for participants who have visited high risk areas in the last 6 months.

k. A COVID-19 test will be performed upon admission to the clinic. Additional COVID-19 tests may be performed if clinically indicated or if needed to comply with clinic and/or local government requirements.

l. PK samples will be collected from all participants for measurement of depemokimab at pre-dose (within 30 minutes prior to injection) and after injection on Day 1 (2 hours and 8 hours [±10 minutes]), Day 2 (24 hours; ±4 hours), Day 3 (48 hours; ±4 hours); Day 5 (96 hours; ±4 hours); Day 8 (±1 day), Day 15 (±1 day); Day 29 (±2 day); Day 57 (±2 day); Day 85 (±3 days); Day 127 (±3 days); Day 169 (±3 days), and Day 183 (±5 days).

m. Any SAEs assessed as related to study procedures or related to a GSK product will be recorded from the time the participant signs the informed consent form to participate in the study.

n. Participants will be allowed to leave the clinic after all study procedures have been completed on Day 3.

o. Windows for clinic visits are as follows: Day 5 (96 hours; ±4 hours); Day 8 (±1 day), Day 15 (±1 day); Day 29 (±2 day); Day 57 (±2 day); Day 85 (±3 days); Day 127 (±3 days); Day 169 (±3 days), and Day 183 (±5 days). There is no visit window applicable for Day 1 to Day 3 as they are in clinic assessments.

p. The last follow-up visit will consist of a telephone call to collect AEs/SAEs and concomitant medications. For WOCBP, this visit will be conducted in clinic so that a pregnancy test result can also be collected.

q. Follow-up call should be attempted if at all possible at Day 211 (W30) when patient early discontinues prior to reaching this time point to ensure patient's safety and well-being.

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.

- The IRB/ IEC will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the ICF. The changes will be approved by the IRB/IEC before implementation.

2. INTRODUCTION

2.1. Study Rationale

This is a single dose study to compare the PK, safety, tolerability, and immunogenicity of a single dose of depemokimab 100 mg administered subcutaneously via a SSD or autoinjector in healthy participants.

This Phase 1 study will be used to compare the PK bioavailability between the SSD and autoinjector.

2.2. Background

Persistent eosinophil inflammation is a feature of more than 50% of patients with severe asthma [Chung, 2014]. Several mAbs targeting eosinophil inflammation have received marketing authorization for asthma with an eosinophilic phenotype, including 3 targeting either IL-5 or IL-5R: mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), and benralizumab (Fasenra). All 3 mAbs, by utilizing blood eosinophils as a biomarker to predict patients likely to respond to therapy, have been shown to reduce asthma exacerbations and improve lung function and health-related quality of life in patients with asthma with an eosinophilic phenotype [Haldar, 2009; Castro, 2011; Pavord, 2012; Bel, 2014; Ortega, 2014; Pavord, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017].

Evidence supporting the tolerability of targeting IL-5/5R has been provided by a well -characterized Phase 3 program [Haldar, 2009; Castro, 2011; Pavord, 2012; Bel, 2014; Ortega, 2014; Pavord, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017] and subsequent long-term extension studies for mepolizumab [Lugogo, 2016; Khatri, 2019; Khurana, 2019], reslizumab [Murphy, 2017], and benralizumab [Busse, 2019] as well as efficacy data from real-world evidence settings for mepolizumab [Harrison, 2020; Bagnasco, 2019; Pertzov, 2019; Schleich, 2020]. Clinical trial data over more than 10 years combined with real-world evidence have demonstrated that treatments targeting the IL-5 pathway are both highly effective and well tolerated. Based on these established efficacy and safety data, anti-IL-5/5R therapies are now a cornerstone of severe asthma management and are endorsed by international guidelines for appropriate patients that continue to exacerbate despite optimized care [GINA, 2020].

Depemokimab is a humanized, affinity matured mAb that blocks human IL-5 by binding to its receptor and belongs to the established class of anti-IL-5 therapies for severe asthma management. Compared with mepolizumab, depemokimab contains 7 amino acid changes in its heavy chain sequence: 4 amino acid changes introduced in the heavy chain variable region and 3 amino acid changes (YTE) introduced in the Fc region. The resulting antibody has increased affinity and half-life. Data indicate that these amino acid changes extend the PK and pharmacology of depemokimab to allow less frequent dosing but are not predicted to alter the safety or efficacy profile of depemokimab relative to mepolizumab (administered chronically).

Long-acting alternatives that can be administered on a less frequent basis are recognized as successful approaches for chronic indications. As a long-acting anti-IL-5 therapy,

depemokimab is anticipated to deliver similar efficacy and safety as currently approved therapies in its class but with a single administration every 26 weeks, as opposed to the current regimen of every 4 weeks for mepolizumab and reslizumab or every 8 weeks for benralizumab (every 4 weeks for the first 3 doses).

GSK has completed a single ascending dose FTIH study to investigate the safety, tolerability, immunogenicity, PK and PD of depemokimab administered subcutaneously in participants with mild-to-moderate asthma, who were controlled on a low-medium daily dose of ICS and/or ICS/ LABAs, and short acting bronchodilators. Eligible participants had a screening blood eosinophil level of ≥200 cells/µL for relevance to the target population and to facilitate investigation of the blood eosinophil profile following single doses of depemokimab.

A detailed description of the chemistry, pharmacology, and safety of depemokimab is provided in the current IB.

For more information, please refer to the depemokimab IB [GSK Document Number 2016N295843_03).

2.3. Benefit/Risk Assessment

Summaries of findings from non-clinical studies conducted with depemokimab and the completed FTIH study 205722 can be found in the current IB. The following section outlines the risk assessment and mitigation strategy for this protocol:

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Depemokimab		
• Allergic reactions including anaphylaxis.	• Allergic reactions, with the most severe form being anaphylaxis (see Appendix 6), are potential risks associated with mAbs. • No allergic reactions or anaphylaxis were reported with depemokimab in FTIH study 205722 in participants with mild-to-moderate asthma. One participant reported an event under the Hypersensitivity standardized MedDRA query with the preferred term of rash verbatim "localized rash both bends of arms" 82 days post 30 mg subcutaneous dose of depemokimab. The event was nonserious, of mild intensity, resolved within 10 days, and was considered unrelated to the study intervention by the investigator.	• Daily monitoring of SAEs by a medical monitor/SAE coordinator; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team. • Use of criteria of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 6). • Use of standardized eCRFs to collect relevant data on systemic reactions. • Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-injection (on Day 1). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of depemokimab, there will be personnel/staff onsite at the clinic who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and they will have access to a system that can promptly transport the participant to another facility for additional care if appropriate. • Participants will be discharged only if the Investigator deems it safe for the participant to leave the clinic.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Type III hypersensitivity (immune complex disease/vasculitis)	• Adverse effects of vascular inflammation consistent with immune complex disease were observed in 1 female monkey in a 1-month toxicity study after administration of 10 mg/kg. Another monkey had a minimal focal inflammation after administration of 100 mg/kg. Immune complex disease was not observed in a 6-month repeat dose (2 doses) study at the same doses. It is unknown if this will translate to humans as preclinical models are not necessarily predictive of clinical findings in humans. • No AEs of Type III hypersensitivity have been reported with depemokimab in FTIH study 205722 in participants with mild-to-moderate asthma (36 participants received depemokimab; 12 participants received placebo).	• Participants with a current diagnosis of vasculitis will be excluded. Participants with high clinical suspicion of vasculitis at screening will be evaluated and excluded from enrollment if diagnosed. • Daily monitoring of SAEs will be done by a medical monitor/SAE coordinator; regular systematic review of AE/SAE data from ongoing studies will be performed by a GSK safety review team. • Protocol guidance on early identification of vasculitis events is provided (see Section 7.1.3).
• Local injection site reactions	• A potential risk of any drug delivered via injection. • No injection site reactions were noted in the preclinical studies. • In the depemokimab FTIH study 205722, injection site reactions were reported by one (3%) participant who received depemokimab and one (8%) participant who received placebo.	• Daily monitoring of SAEs by a medical monitor/SAE coordinator; regular systematic review of AE/SAE data from ongoing studies by a GSK study team and/or GSK safety review team. • Use of standardized eCRFs to collect relevant data on local injection site reactions.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• QTc prolongation	• Four monkeys in the 6-month repeat dose monkey study administered 100 mg/kg every 3 months (2 doses) were observed to have QTc prolongation (mean change of 18 msec relative to the vehicle control value) during Week 14. • In the depemokimab FTIH study (205722), no treatment effect on the ECG parameters including QTcF was observed across the depemokimab treatment groups (n=36). No participants met QTcF protocol specified criteria (QTcF >500 msec or increase from baseline >60 msec, or uncorrected QT >600 msec) that would have required additional monitoring. • Analysis of the relationship between depemokimab plasma concentrations and change from baseline QTcF data collected in FTIH study (205722) did not reveal any clinically or statistically significant trends of concern with an increasing depemokimab dose up to 300 mg. The predicted increase in mean QTcF change from baseline with depemokimab plasma concentrations point estimates remained below 10 msec [DHHS, 2005] up to concentrations of 100 ug/mL, with a 95% lower CI consistent with zero change from baseline (i.e. the 95% lower bound of the CI was below zero) [GSK Document Number: 2020N457410_00].	• ECGs will be performed according to time points specified in the SoA (Section 1.3) and the assessments will be done as specified in Section 8.3.3. • Participants with QTc prolongation at screening will be excluded (criterion 19, Section 5.2.4. • Participants with a pre-existing clinically significant cardiac medical condition are excluded (criterion 1, Section 5.2.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Immunogenicity, antidrug antibodies (ADAs)	• Biopharmaceutical products may elicit ADAs and NAb, which have the potential to modulate PK or pharmacodynamics (PD), or to produce adverse reactions. • In FTIH study 205722, none of the participants tested positive for ADA at baseline. Overall, 9 participants (25%) had confirmed positive results for ADA at any time post-baseline, primarily in the depemokimab 30 mg dose group (5 participants), which was also the group with the highest total serum IL-5 concentrations. This apparent correlation warrants further investigation. There were no major differences observed in the depemokimab plasma concentration profiles and blood eosinophil count-time profiles as well as AE reporting between ADA-positive and ADA-negative participants. Neutralizing antibodies were not tested in this study.	• Blood samples will be collected for detection of both ADA and NAb (see Section 8.9).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Risk of depemokimab affecting an unborn baby	• Reproductive studies have not been conducted with depemokimab; however, in the 6-month repeat dose monkey study no changes were observed in reproductive organs. Seminiferous tubules were evaluated with respect to their stage in the spermatogenic cycle and the integrity of the various cell types present within different stages in sexually mature males. No cell- or stage-specific abnormalities were noted. • In addition, there is a low reproductive risk associated with the IL-5 target mechanism (as shown in preclinical reproductive toxicology studies of mepolizumab and reslizumab), a low genotoxic concern for mAbs in general, and a low transfer of mAbs into semen due to the inability of large molecular weight proteins such as depemokimab to access pivotal cells in the testes [Setchell, 1975; Pollanen, 1995; Pollanen, 1989; Setchell, 2001; Sohn, 2016]; the risk of adverse effects on spermatogenesis is considered minimal. Therefore, male participants are not required to use contraception.	• Participants who are pregnant, breastfeeding, or plan to become pregnant at screening are excluded from the study. • All female participants will be assessed at screening to determine childbearing status. Female participants of childbearing potential must be using a highly effective contraceptive method from at least 14 days prior to administration of the study intervention until at least 30 weeks after administration.
Study Procedures		
• Potential risk for injury with phlebotomy	• Risks with phlebotomy include bruising, bleeding, infection, and nerve damage.	• Procedures to be performed by trained personnel (i.e., study nurse).

ADA = antidrug antibodies; AE = adverse event; CI = confidence interval; CRF = case report form; ECG = electrocardiogram; FTIH = first time in human; MAb = monoclonal antibodies; NAb = neutralizing antibodies; NIAID/FAAN = Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network; MedDRA = Medical Dictionary for Regulatory Activities; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QTc = QT interval corrected for heart rate; QTcF = QT interval corrected by Fridericia's formula; SAE = serious adverse event; SoA = schedule of activities

2.3.2. Benefit Assessment

Since this Phase 1 study is being conducted in healthy adult participants, there is no direct clinical benefit to study participants.

2.3.3. Overall Benefit-risk Conclusion

Although no clinical benefit is expected for recruited participants, overall the benefit:risk balance for this PK study is considered acceptable based on available data from the FTIH study and risk mitigation strategy implemented for this protocol. The study provides the opportunity to compare the PK, safety, tolerability, and immunogenicity of a single dose of depemokimab 100 mg administered subcutaneously via a SSD and AI

Taking into account the measures taken to minimize risk to participants enrolled in this study, the potential risks identified in association with depemokimab are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the relative bioavailability of subcutaneous depemokimab following a single dose delivered with a SSD or an autoinjector in healthy adult participants	• Cmax and AUC(0-inf) of depemokimab in plasma
Secondary	
• To assess additional PK parameters following a single dose of depemokimab delivered with a SSD or an autoinjector in healthy adult participants	• AUC(0-t), Tmax, CL/F, Vd/F, λz, T1/2, Tlast, and %AUCex of depemokimab in plasma
• To assess the immunogenicity of a single dose of depemokimab delivered with a Safety Syringe Device or an autoinjector in healthy adult participants	• Incidence of immunogenicity as measured by the presence of antidrug antibodies and neutralizing antibodies to depemokimab
Safety	
• To assess the safety profile following a single dose of depemokimab delivered with a Safety Syringe Device or an autoinjector in healthy adult participants	• Incidence of adverse events and serious adverse events • Change from baseline in laboratory parameters (including hematological and clinical chemistry parameters) and hepatobiliary laboratory abnormalities at discrete time points during the 26-week period • Change from baseline in vital signs (heart rate, systolic and diastolic blood pressure, body temperature) at discrete time points during the 26-week period • Change from baseline in electrocardiogram values at discrete time points during the 26-week period
Exploratory	
• To evaluate depemokimab pharmacodynamic effects on blood eosinophil count following a single subcutaneous dose with Safety Syringe Device or an autoinjector in healthy adult participants	• Ratio to baseline in blood eosinophil count over time

Objectives	Endpoints
• Device functionality	• User and device errors
• To compare the pharmacokinetics of subcutaneous depemokimab following a single dose administered in the upper arm, thigh, or abdomen	• Depemokimab measured concentration at planned visits, by anatomical site of injection • Cmax and AUC(0-inf) of depemokimab in plasma, by anatomical site of injection

%AUCex = percentage of AUC(0-inf) due to extrapolation from Tlast to infinity; AUC(0-inf) = area under the concentration-time curve from time zero extrapolated to infinity; AUC(0-t) = area under the concentration-time curve from time zero to time of last observed quantifiable concentration; CL/F = apparent clearance following extravascular administration; Cmax = maximum observed plasma concentration; λz = terminal elimination rate constant; PK = pharmacokinetic(s); T1/2 = terminal elimination half-life; Tlast = time of last measurable plasma concentrations; Tmax = time to maximum observed plasma concentration; Vd/F = apparent volume of distribution following extravascular administration.

Primary Estimand:

The primary question of interest is: to assess the relative bioavailability (assessed as ratio of the geometric mean of PK parameters maximum observed plasma concentration [Cmax] and area under the concentration-time curve from time zero extrapolated to infinity [AUC(0-inf)]) of a single dose of depemokimab delivered with a SSD versus an autoinjector in healthy adult participants.

The primary PK estimand is described by the following attributes:

- Population: Healthy male and female participants 18 to 50 years of age inclusive.
- Treatment condition: Single subcutaneous dose of 100 mg depemokimab administered via a SSD versus single subcutaneous dose of 100 mg depemokimab administered via an autoinjector.
- Variable:
  - Cmax and AUC(0-inf).
- Summary measure:
  - Ratio of the geometric mean of SSD versus autoinjector for Cmax and AUC(0-inf).
- Intercurrent events:
  - Use of prohibited medication: Use of prohibited medication is not expected to impact the PK of depemokimab; therefore, treatment policy strategy will be used and the individual PK concentrations after the occurrence of the intercurrent event will still be included into PK analysis.
- Handling of missing data:
  - For participants that withdraw prior to Week 18, or no PK concentrations are available until Week 18, it is anticipated that it will not be possible to derive the PK parameter AUC(0-inf). The participant will be excluded from the analyses related to AUC(0-inf) and no missing data imputation will be performed.

- For participants that withdraw prior to Week 4, or no PK concentrations are available until Week 4, it is anticipated that it will not be possible to derive a meaningful value for the PK parameter Cmax. The participant will be excluded from the analyses related to Cmax and no missing data imputation will be performed.

- Rationale for Estimand:
  - Use of prohibited medications is not expected to impact the PK of depemokimab.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, multicenter, open-label, parallel-group, single-dose study in healthy adult participants. A single subcutaneous dose of depemokimab will be administered via a SSD or an autoinjector.

The study will consist of a screening period, one treatment period, and a follow-up period.

Participants will be randomly assigned in a 1:1 ratio to receive 1 of 2 treatments during the treatment period as follows:

- Treatment A: a single subcutaneous dose of 100 mg depemokimab administered via a SSD
- Treatment B: a single subcutaneous dose of 100 mg depemokimab administered via an autoinjector

The randomization will be stratified by body weight (<70 kg, 70 to <80 kg, and ≥80 kg). The site of injection will be randomized in a 1:1:1 ratio to the upper arm, abdomen, or thigh. All treatments will be administered by authorized study site staff.

Participants will be screened within 30 days before the first dose of study intervention. Each participant will receive a single subcutaneous dose of depemokimab on Day 1 and will then be observed. Participants may be discharged from the clinic after all study procedures have been completed on Day 3. Participants will return for outpatient visits and receive a follow-up telephone call approximately 211 days after study intervention administration.

Study assessments will be performed as indicated in the SoA (Section 1.3) Pharmacokinetic blood samples for the analysis of depemokimab will be collected prior to dosing on Day 1 and up to Day 183 after dosing.

Safety and tolerability will be assessed by the monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, and 12-lead ECG results.

Including screening and the follow-up period, the total duration of the study is approximately 241 days.

4.2. Scientific Rationale for Study Design

A healthy participant population is considered to be suitable for the evaluation of depemokimab PK comparability among treatments. Healthy participants are considered to be a suitable population for biopharmaceutical PK comparability studies, and the data can be extrapolated to other populations.

Depemokimab has a prolonged half-life of approximately 6 weeks, and a crossover design would require an extended washout period that would limit recruitment and likely lead to significant drop-outs and is therefore considered inappropriate. A parallel-group design in healthy participants is the typical approach for such studies with monoclonal antibodies and has been successfully used for a number of similar products.

To minimize the impact of potential confounding factors and variability, the study will be stratified by body weight as this is the main covariate of depemokimab exposure, although the effect is not large enough to be clinically relevant. To investigate the effect of injection site, depemokimab will be administered by the study site staff at 1 of 3 injection sites (upper arm, abdomen or thigh). In order to prevent bias as well as maintain balance in treatment groups, the injection site will be randomized. Collection of PK blood samples up to Day 183 will ensure that the depemokimab plasma concentration-time profile is well described with the extrapolated portion of AUC(0-inf) well below 20%.

4.2.1. Participant Input into Design

Not applicable.

4.3. Justification for Dose

A single depemokimab dose of 100 mg administered subcutaneously is selected in this study as it is the dose under study and the anticipated therapeutic dose for severe asthma with an eosinophilic phenotype. The anticipated therapeutic dose in other eosinophilic diseases is currently expected to be either 100 mg or multiples of 100 mg, administered as single or multiple injections of 100 mg each. This study is planned to support use and approval of the autoinjector in all eosinophilic indications, for which the dose is expected to be administered as one or multiple injections of 100 mg.

4.4. End-of-study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study.

A participant is considered to have completed the study if he or she has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. The study population will consist of adult participants from 18 to 50 years of age inclusive at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, clinical laboratory tests, vital sign measurements, and 12-lead ECG results. A participant with a clinical abnormality or laboratory parameters outside the reference range may be included only if the investigator (in consultation with the medical monitor, if necessary) documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

Weight

3. Body weight ≥50 kg (110 lbs) and body mass index within the range 19 to 30 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

4. Male or female

a. Male Participants: as depemokimab is a monoclonal antibody that is not anticipated to interact directly with DNA or other chromosomal material with minimal exposure through semen expected, male participants will not be required to use contraception during the study, nor are they prohibited from donating sperm.

b. Female Participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
    - Is not a WOCBP as defined in Appendix 4

      OR

    - Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4, from at least 14 days prior to administration of the study intervention until at least 30 weeks after administration
- A WOCBP must have a negative highly sensitive serum pregnancy test at screening and a negative highly sensitive urine pregnancy test within 24 hours before study intervention. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be

excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing are located in Section 8.3.5.

- Contraceptive use by WOCBP should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention).
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

5.2.1. Medical Conditions

1. History or presence of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs, constituting a risk when taking the study intervention, or interfering with the interpretation of data.
2. Hypersensitivity: Participants with allergy/intolerance to a monoclonal antibody or biologic or any of the excipients of the investigational products listed in Section 6.1, or participants with a previous history of clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
3. Parasitic infection: Participants with a known, pre-existing parasitic infection within 6 months prior to screening or a positive test for parasite screening. Note: Parasite testing is only required for participants from high risk areas as deemed applicable by the investigator.
4. Vasculitis: Participants with a current diagnosis of vasculitis. Participants with high clinical suspicion of vasculitis at screening will be evaluated and any occurrence of vasculitis will be exclusionary.
5. Abnormal and clinically significant blood pressure as determined by the investigator or designee.
6. Any surgical or medical condition (active or chronic) that may interfere with drug absorption, distribution, metabolism, or excretion of the study intervention, the

interpretation of study data or any other condition that may place the participant at risk, in the opinion of the investigator.

7. Positive test for severe acute respiratory syndrome coronavirus (SARS-CoV-2) at **any time during the screening period prior to admittance to the CRU**. Note: Testing will be performed according to site procedures.

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

9. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.

5.2.2. Prior/Concomitant Therapy

10. Participants must abstain from taking prescription or non-prescription drugs (except for acetaminophen [up to 2 grams per day]), vitamins, and dietary or herbal supplements, unless specified in Section 6.8, within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with study procedures or compromise participant safety. Any exceptions will be discussed with the sponsor or medical monitor on a case-by-case basis and the reasons will be documented.

5.2.3. Prior/Concurrent Clinical Study Experience

11. Previous exposure to depemokimab within 12 months prior to starting study intervention.

12. Participant has donated blood in excess of 500 mL within 12 weeks prior to dosing or participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.

13. Treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.

14. Exposure to more than 4 new chemical entities within 12 months prior to the dosing day.

15. Current enrollment or past participation in another investigational study in which an investigational intervention (e.g., drug, vaccine, invasive device) was administered within 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) before signing of consent in any other clinical study involving an investigational study intervention or any other type of medical research.

5.2.4. Diagnostic Assessments

16. Presence of hepatitis B surface antigen, or positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention.

17. Alanine aminotransferase (ALT) >1.5 × ULN at screening or check-in. A single repeat of ALT is allowed within a single screening period to determine eligibility.

18. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening or check-in. A single repeat of any laboratory abnormality is allowed within a single screening period to determine eligibility.
19. QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec.
20. A known immunodeficiency.
21. A positive test for human immunodeficiency virus antibody.
22. History of regular alcohol consumption within 6 months of screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or an average weekly intake of >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 270 mL of full-strength beer, 470 mL of light beer, 30 mL of spirits, or 100 mL of wine.
23. A positive test result for drugs of abuse (including marijuana) or alcohol at screening or Day –1.

5.2.5. Other Exclusion Criteria

24. Participant has a dermatological condition or artifact (e.g., tattoo) at any of the injection sites that reduces the ability to evaluate the sites for AEs, in the opinion of the investigator.
25. Participant is unable to comply with all study procedures, in the opinion of the investigator.
26. Participant should not participate in the study, in the opinion of the investigator or sponsor.

5.3. Lifestyle Considerations

5.3.1. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine or xanthine containing products (e.g. coffee, tea, cola drinks and chocolate) for 6 hours prior to the start of dosing and 6 hours prior to ECG recordings.

- Participants will abstain from alcohol for 24 hours before the start of dosing and must have a negative alcohol test at check-in (Day –1).

- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches and other delivery devices such as vaporizers) will not be permitted while they are in the clinical unit.

5.3.2. 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 study confinement (e.g., watching television, reading).

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized and entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, information from any previous trials with depemokimab, any protocol deviations, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/administration of Study Intervention

Not applicable for this study.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s)/products, 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

The study intervention administered in this study are described in Schedule of Activities (SoA) Table 1. A description of the study treatments is included in Table 2.

Depemokimab (GSK3511294) is a humanized immunoglobulin G (IgG) antibody (IgG1, kappa) with human heavy and light chain frameworks. Depemokimab liquid drug product will be supplied by GSK in a Type I glass syringe (with a 1/2-inch, 29-gauge thin wall, staked needle and sealed with a latex free rubber plunger). The drug product and syringe will be assembled in a single-use, disposable safety syringe or an autoinjector to enable delivery of the drug product. Each device enables subcutaneous delivery of 100 mg GSK3511294 in 1.0 mL sterile liquid formulation. The formulation contains L-histidine, trehalose dihydrate, L-arginine hydrochloride, EDTA, water for injection and polysorbate 80.

Table 3 Study Intervention(s) Administered

Intervention Label	Depemokimab	Depemokimab
Intervention Name	Depemokimab	Depemokimab
Intervention Description	Subcutaneous via SSD	Subcutaneous via autoinjector

Type	Biologic	Biologic
Dose Formulation	Sterile liquid formulation in single-use Safety Syringe Device	Sterile liquid formulation in single-use autoinjector
Unit Dose Strength(s)	100 mg/mL; 1.0 mL (deliverable)	100 mg/mL; 1.0 mL (deliverable)
Dosage Level(s)	100 mg once on Day 1	100 mg once on Day 1
Route of Administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Experimental
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in SSD. Each SSD will be labeled as required per country requirement.	Study intervention will be provided in an autoinjector. Each autoinjector will be labeled as required per country requirement.

AxMP = Auxiliary medicinal product; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; SSD = pre-filled safety syringe

Table 4 Study Arm(s)

Arm Title	A	B
Arm Type	Experimental	Experimental
Regimen number		
Arm Description	Participants will receive a single subcutaneous 100 mg dose via SSD on Day 1.	Participants will receive a single subcutaneous 100 mg dose via autoinjector on Day 1.

SSD = Safety Syringe Device

6.1.1. Medical Devices

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

- A pre-filled syringe is contained within a Safety Syringe Device or an autoinjector. The devices used in the study are representative of the devices planned to be marketed for the product.

- The components that comprise the pre-filled syringe (glass barrel with pre-staked needle and plunger stopper) are sourced from Becton Dickinson. The syringe is filled with study intervention (depemokimab) and assembled into a Safety Syringe Device or an autoinjector at GSK, Barnard Castle.
- The Safety Syringe Device components are manufactured by Becton Dickinson. The safety syringe components are assembled with the pre-filled syringe at GSK, Barnard Castle.
- The autoinjector components are manufactured by Ypsomed. The autoinjector components are assembled with the pre-filled syringe at GSK, Barnard Castle.

The IFU for these medical devices will be provided. The instructions were developed and optimized as a result of formative human factors studies for mepolizumab and support the proper use of the depemokimab SSD and autoinjector.

All device deficiencies, (including malfunction, use error, and inadequate labeling) shall be documented, and reported by the investigator throughout the clinical investigation (see Sections 8.4.7 and Section 10.7) and appropriately managed by the sponsor.

All defective devices will be returned to GSK. Details can be found in the SRM.

6.2. Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention. If allowed by country regulation/ethics, study intervention may be administered by a HHS professional.
- All study intervention 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.
- The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet MSDS/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Blinding and Assignment to Study Intervention

6.3.1. Blinding:

This is an open-label study.

6.3.2. Assignment to Study Intervention:

Eligible participants will be randomly assigned to a treatment in accordance with the randomization schedule generated from the IRT system at GSK prior to the start of the study. Participants will be assigned to study intervention in accordance with the randomization schedule. Once a randomization number has been assigned to a participant, it cannot be reassigned to any other participant in the study.

Participants will be randomly assigned to receive 1 of 2 treatments with a ratio of 1:1 during the treatment period on Day 1 (Hour 0). Randomization will be stratified according to the participant's baseline body weight (<70 kg, 70 to <80 kg, and ≥80 kg). The site of injection will also be randomized in a 1:1:1 ratio to the upper arm, abdomen, or thigh. All treatments will be administered by authorized study site staff

6.4. Study Intervention Compliance

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

Participants will be monitored at the site for a minimum of 2 hours after depemokimab dosing to monitor for immediate hypersensitivity and any other untoward effects. In the event of an acute severe reaction (e.g., anaphylaxis), there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate.

6.5. Dose Modification

There are no specific adjustment/stopping criteria for this study. Each participant will receive a single dose of depemokimab 100 mg subcutaneously via SSD or autoinjector in this study.

6.6. Continued Access to Study 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.

6.7. Treatment of Overdose

The dose of depemokimab that is considered to be an overdose has not been defined. There are no known antidotes and there is no specific treatment for a suspected overdose. In FTIH

study 205722 (refer to the GSK3511294 IB [GSK Document Number 2016N295843_03]), single subcutaneous doses of depemokimab up to 300 mg were well tolerated by adult participants with mild/moderate asthma (6 participants received a 300 mg subcutaneous dose).

Each SSD and autoinjector will enable the delivery of a 100 mg single dose of study intervention (see Section 6.1).

In the event of an overdose, the investigator should:

1. Treat the participant with active supportive care as dictated by the participant's clinical status in the knowledge of the long half-life (approximately 41 days) of depemokimab.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities for 30 weeks following the last administered dose.
3. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.8. Prior and Concomitant Therapy

Participants must abstain from taking prescription or non-prescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study procedures or compromise participant safety.

Paracetamol (acetaminophen), at doses of ≤ 2 grams/day, is permitted for use any time during the study.

Any concomitant medications (e.g., vaccines) may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required. (Note: Any approved coronavirus disease 2019 (COVID-19) vaccine is permitted, but participants should avoid receiving the vaccination within 14 days of depemokimab dosing. If vaccination within 14 days is unavoidable, then an alternative time interval can be considered on a case-by-case basis in conjunction with the medical monitor. Experimental COVID-19 vaccines are not permitted.)

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 enrollment or receives during the study must be recorded in the eCRF along with:

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

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1.

7.1. Discontinuation of Study Intervention

There are no specific discontinuation of study intervention criteria for this study. Each participant will receive a single dose of depemokimab 100 mg subcutaneously in this study.

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. Since this is a single dose study, liver chemistry stopping criteria do not apply. If the following criteria are met, increased liver monitoring is required:

- ALT ≥ 3× ULN
- ALT ≥ 3× ULN AND bilirubin ≥ 2× ULN (>35% direct bilirubin) or INR > 1.5

See Appendix 5 for guidance regarding increased monitoring of liver chemistry and required actions and follow-up assessments.

7.1.2. QTc Stopping Criteria

Since this is a single dose study, QTc stopping criteria do not apply.

A detailed assessment including a concomitant assessment for PK, renal chemistry and electrolytes (potassium, calcium, and magnesium), toxicology screen, and clinical evaluation (e.g., continuous cardiac monitoring, admission for direct observation or referral) and discussion with the medical monitor will be triggered in the following scenarios:

Refer for appropriate monitoring and treatment as per local protocol:

- Arrhythmia or evidence of clinical impact e.g., syncope.
- QTcF change from baseline > 60 msec and no clinical impact. (Baseline is the average of triplicate readings at pre-dose on Day 1).
- QTcF > 500 msec or uncorrected QT > 600 msec and no clinical impact.

Note: the QTcF should be based on averaged QTcF values of triplicate ECGs obtained over a brief (up to 10 minutes) recording period.

7.1.3. Criteria for Follow-up of Potential Type III Hypersensitivity (Immune Complex Disease/Vasculitis)

Due to the adverse findings of arterial inflammation that were observed in the 1-month, but not the 6-month, non-clinical toxicology studies, events potentially representing Type III hypersensitivity/immune complex disease/vasculitis should be promptly reported to GSK, and consultation with the medical monitor is encouraged. Treatment for the event will be given as medically required. If possible, PK, ADA, C3, and C4 samples may be taken at the time of the event along with hematology, clinical chemistry and urinalysis samples.

Symptoms potentially suggestive of vasculitis include but are not limited to:

- persistent* fever
- persistent* muscle and joint pain
- persistent* rash
- persistent* fatigue
- symptoms of peripheral neuropathy, such as numbness or weakness
- laboratory abnormalities, e.g., decreased platelet counts, elevated creatinine, decrease in complement C3/C4, abnormal urinary albumin/creatinine ratio

Note: *where persistent is considered to be a duration of ≥ 2 days

Participants who experience any of the above events should be monitored until the event resolves and/or a diagnosis is established.

The symptoms and clinical features are often non-specific and heterogenous with respect to the time course over which they develop, organ involvement, and the constellation of symptoms and severity. Early recognition of potential events of vasculitis is important for timely diagnosis and subsequent treatment.

The precise management will depend on the clinical evaluation at the time of presentation and ongoing assessment including consideration of relevant differential diagnoses. Given that there is often a differential for presenting symptoms, such as infection, and that such factors may also precipitate immune-related AEs, these factors (infectious, neoplastic, metabolic, toxic) should be given due consideration and ruled out.

Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis, and consultation with the medical monitor and an appropriate medical specialist should be considered when investigating a possible immune-related AE.

Unscheduled PK, ADA, C3, and C4 samples may be taken at the time of the event and samples may be taken for additional biomarkers (e.g., ANA, ANCA) in the setting of clinical concern regarding the possibility of immune complex disease. If necessary, testing for biomarkers, e.g., ANA, ANCA (anti- MPO antibody and anti- PR3 antibody), may also be conducted using the frozen baseline serum samples (that were collected and stored prior to administration of study intervention) to allow for evaluation of interval change for participants with suspected vasculitis (see Section 8.9). Other possible causative or

differential factors for abnormal clinical or laboratory observations may also have to be investigated including testing to exclude infection.

If clinically indicated, the participant may be referred to a specialist for further management, which may include organ biopsy.

7.2. Participant Discontinuation/Withdrawal from the Study

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

7.3. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

At the time of discontinuing from the study, if possible, an ED visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. 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, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for participant discontinuation/ withdrawal from the study will be documented in the eCRF based on the list below:

Reasons	Additional items/Sub-reasons
AE	
Lack of efficacy	
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify
Physician Decision	Clinical relapse Other, Specify
Progressive disease*	
Protocol Deviation	Specify
Site Terminated by Sponsor	Specify
Sponsor terminated study treatment	
Study Terminated by Sponsor	
Subject reached protocol-defined stopping criteria	Liver Chemistry Stopping Criteria QTc Stopping Criteria Severe allergic reaction/anaphylaxis Vasculitis (Type III hypersensitivities reaction)
Withdrawal by Participant	Burden of Procedure Subject relocated Other, Specify
Death**	

* Present on Study Treatment Discontinuation Form and not on Study Conclusion Form.
** Present on Study Conclusion Form not on Study Treatment Discontinuation Form.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.3.5).

7.4. Lost to Follow-up

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (SoA). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness
- 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. Subjects who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within the timeframe defined in the SoA. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The maximum amount of blood collected from each participant over the duration of the study, including extra assessments that may be required, will not exceed approximately 300 mL.

8.1. Administrative Procedures

Not applicable.

8.2. Efficacy Assessments

Not applicable. This study is an open-label single dose PK study in healthy participants. There is no efficacy outcome for this study.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

Additional time points for safety tests (such as vital sign measurements, physical examinations, and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring

8.3.1. Physical Examination

- A complete physical examination will include, at a minimum, assessments of the skin and cardiovascular, respiratory, gastrointestinal, and neurological systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

- Brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

8.3.2. Vital Signs

- Temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate will be assessed.
- Blood pressure and pulse measurements will be assessed in the resting state (sitting or supine) with a completely automated device. Manual techniques will be used only if an automated device is not available. The site will follow their standard process for repeating vital signs, as needed.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Blood pressure and pulse will be measured in triplicate before dosing; single measurements after dosing. Single temperature and respiratory rate measurements will be measured at all time points.
- At each time point at which triplicate measurements are required, 3 consecutive blood pressure and pulse readings will be recorded at intervals of at least 1 minute. Each measurement will be recorded in the eCRF.
- When vital signs are scheduled at the same time as blood collections for laboratory assessments, vital signs are to be taken first.

8.3.3. Electrocardiograms

- Twelve-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates heart rate and measures PR, QRS, QT, and QTcF intervals.
- Twelve-lead ECGs will be performed with the participant in a semi-supine position after a rest of at least 10 minutes.
- Triplicate ECGs are required at baseline prior to dosing, and 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 over a brief (e.g., 5 to 10 minutes) recording period.
- Screening ECGs are single measurement except if QTc > 450 msec, in which case triplicate measurements are expected and the average of the 3 measurements should be considered. This exception also applies to a case of arrhythmia or evidence of clinical impact (Section 7.1.2).
- Post-dose ECGs are single assessments. Refer to Section 7.1.2 for potential exceptions.

8.3.4. Clinical Safety Laboratory Tests

- All protocol-required safety laboratory assessments will be conducted at the clinic's local laboratory. See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. Reference ranges for all safety parameters will be provided to GSK by the laboratory responsible for the assessments.

- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study 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 clinically significant 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 tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.5. Pregnancy Testing

Refer to Section 5.1 for pregnancy testing entry criteria.

A serum pregnancy test should be conducted for all WOCBP at screening and at study exit/early termination. In addition, a highly sensitive urine pregnancy test should be performed for all WOCBP at the specified scheduled study visits per the SoA, and at the follow-up visit (Section 1.3).

Pregnancy test for WOCBP is marked for a last follow-up visit (W30/ D211) while this is expected to be a phone assessment, not in clinic visit. However, only WOCBP participants will perform this visit in clinic and a highly sensitive urine pregnancy test will be performed. Male and non-WOCBP participants will complete the visit remotely via phone assessment as stated in the current protocol.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In case of positive serum pregnancy result during the screening or at the time of enrollment, the participant must be excluded from participation in the study. If pregnancy test comes back positive at any time during the study, after the administration of the study intervention, the participant should be encouraged to remain in the study to continue with

the safety assessments. Additionally, the pregnancy should be reported and additional follow-up information collected per Section 8.3.5.

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

The definitions of AEs or SAEs can be found in Section 10.3.

The definitions of device-related safety events, ADEs, SADEs, and device deficiencies can be found in Section 10.7.

Adverse events will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all events (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All AEs/SAEs will be collected from the start of intervention until the last visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.
- All SAEs will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.4.4. AESIs

Adverse events of special interest include:

- Allergic reactions including anaphylaxis

Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 NIAID/ FAAN Second Symposium on Anaphylaxis [Sampson, 2006] (Appendix 6)

- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation

See Section 2.3.1 for additional details.

8.4.5. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an 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, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.6. Pregnancy

- Details of all pregnancies in female participants will be collected after administration of study intervention and until 30 weeks after the administered dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.5. 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.

8.4.7. Medical Device Deficiencies

Medical devices (SSD and autoinjector) are being provided for use in this study as a delivery method for depemokimab injections. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

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

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

8.4.7.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a device deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Section 10.7.

8.4.7.2. Follow-up of Medical Device Deficiencies

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

8.4.7.3. Prompt Reporting of Medical Device Deficiencies to the Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The Medical Device Deficiency Report Form will be sent to the sponsor by email. If email is unavailable, then fax should be utilized.
- The sponsor will be the contact for the receipt of device deficiency reports.

8.4.7.4. Regulatory Reporting Requirements for Device Deficiencies

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

8.5. Pharmacokinetics

8.5.1. Blood Sample Collection

Blood samples for determination of depemokimab plasma concentrations will be collected at the time points indicated in the SoA (Section 1.3). Each PK sample must be collected as close as possible to the planned time relative to when the dose is administered to the participant (which is 0 hour on Day 1). The actual date and time of each blood sample collection will be recorded in the eCRF.

Details on PK blood sample collection, processing, storage, and shipping procedures will be provided in the SRM.

8.5.2. Sample Analysis

Sample analysis will be performed under the control of BIB, GSK. Concentrations of depemokimab will be determined in plasma samples using a validated bioanalytical method.

8.6. Pharmacodynamics

Pharmacodynamics are not evaluated in this study

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Antibodies to depemokimab will be collected at the time points specified in the SoA (Section 1.3). The actual date and time of each blood sample will be recorded. Details for immunogenicity blood sample collection, processing, storage, and shipping will be provided in the SRM.

Sample analysis will be performed under control of BIB, GSK. The presence of anti-depemokimab antibodies will be determined in serum samples using a validated bioanalytical method, with a tiered analyses approach using a screening assay, confirmation assay, and titer assay and a validated NAb assay. If necessary, further immune response characterization may be performed as needed.

8.10. Health Economics OR Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This study is designed to estimate the relative bioavailability of depemokimab 100 mg administered subcutaneously via an autoinjector compared to a SSD. No formal hypotheses will be tested. For Cmax and AUC(0-inf), point estimates and corresponding two-sided 90% CIs will be constructed for the ratio of the geometric mean of the autoinjector to SSD.

An additional assessment will be made by comparing observed 90% CI of geometric mean ratio to the standard bioequivalence reference range of 0.8 to 1.25.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Population	Definition/Criteria
Screened	All participants who are screened.
Safety	All participants who take at least 1 dose of study intervention. Participants will be analysed according to the intervention they actually received.
Pharmacokinetic	All participants in the Safety Population for whom at least 1 evaluable pharmacokinetic sample will be obtained and analysed. Participants will be analysed according to the intervention they actually received.

9.3. Statistical Analyses

9.3.1. General Considerations/Definitions

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints.

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

Pharmacokinetic Analysis

Plasma depemokimab concentration-time data will be analysed by PPD, under the oversight of the Clinical Pharmacology Modeling & Simulation department within GSK, using noncompartmental methods with Phoenix WinNonlin Version 8.0 or higher. Statistical analysis will be performed by Veramed, under the oversight of Biostatistics, GSK. Calculations will be based on the actual sampling times recorded during the study.

Based on the individual concentration-actual time data the following PK parameters will be estimated as data permit:

- AUC(0-inf) – Area under the concentration-time curve from time zero extrapolated to infinity

- AUC(0-t) – Area under the concentration-time curve from time zero to time of last observed quantifiable concentration
- Cmax – Maximum observed plasma concentration
- Tmax – Time to maximum observed plasma concentration
- CL/F – Apparent clearance following extravascular administration
- Vd/F – Apparent volume of distribution following extravascular administration
- λz – Terminal elimination rate constant
- t1/2 – Terminal elimination half-life
- Tlast – Time of last measurable plasma concentrations
- %AUCex – Percentage of AUC(0-inf) due to extrapolation from Tlast to infinity

Pharmacokinetic data will be presented in graphical and/or tabular form and will be listed and summarized descriptively by treatment group, and by injection site.

Endpoint	**Statistical Analysis Methods**
Primary	The analysis for the primary PK endpoints will be performed for the PK Population. Pharmacokinetic analysis will be performed to compare the relative bioavailability of a single subcutaneous dose of 100 mg depemokimab administered via an autoinjector compared to a single subcutaneous dose of 100 mg depemokimab administered via SSD. Based on the individual concentration-time data the following primary plasma PK parameters will be estimated: Cmax and AUC(0-inf) Analysis will be performed on the natural logarithms of AUC(0-inf) and Cmax using a fixed-effects analysis of covariance model, with treatment and injection site as categorical covariates, and baseline weight as a continuous covariate fitted on the log scale. Effects will be estimated, and 90% CIs will be constructed for the following treatment comparisons: Treatment B (Autoinjector) versus Treatment A (SSD) Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale.
Secondary	The analysis for the secondary PK endpoints will be performed for the PK Population.

Endpoint	Statistical Analysis Methods
	Summary statistics for AUC(0-t), CL/F, Vz/F, λz, and t1/2, (arithmetic mean, geometric mean, median, 95% CI [arithmetic and geometric], standard deviation [arithmetic and on ln-scale], minimum, maximum, and geometric CV). For Tmax and Tlast, median, minimum, and maximum only will be reported for each treatment group.

Further details of the PK analysis are provided in the SAP.

9.3.3. Safety Analyses

All safety analyses will be performed on the Safety Population.

Summaries of safety data will include AEs, SAEs, change from baseline of vital signs, ECGs, and laboratory parameters along with hepatobiliary abnormalities. Adverse events will be coded using the MedDRA coding dictionary and will be grouped by SOC and summarized by preferred term and treatment. Adverse events will be summarized by frequency and percentage of participants, by SOC and preferred term within each group. Separate summaries will be provided for all AEs, drug-related AEs, SAEs, and AEs leading to withdrawal from the study.

The positive rate of ADAs following a 100 mg depemokimab before and after administration will be summarized and listed based on the safety population. Details will be presented in the SAP.

9.3.4. Exploratory Analysis

To assess the pharmacodynamics of a single subcutaneous dose of depemokimab delivered with a safety syringe or an autoinjector in healthy adult participants, the ratio to baseline of the eosinophil count will be summarized by treatment group with descriptive statistics.

To assess the pharmacokinetics of a single subcutaneous dose of depemokimab delivered in the upper arm, abdomen, or thigh in healthy adult participants, the measured depemokimab plasma concentration at planned visits will be summarized with descriptive statistics. Additionally, a fixed-effects analysis of covariance model, with treatment and injection site as categorical covariates, and baseline weight as a continuous covariate fitted on the log scale and including an interaction term between treatment and injection site will be performed for the primary PK endpoints.

User and device errors will be summarized using appropriate descriptive statistics.

9.4. Interim Analysis

No formal interim analysis is planned; however, if recruitment is significantly slower than anticipated, then a single interim analysis may be conducted to assess variability, and which could result in a re-estimation of the sample size.

Available PK concentration data from completed participants may be inspected to support development of depemokimab PK model . No changes to the conduct of the study will be implemented as a result of these analyses.

9.5. Sample Size Determination

A total of approximately 126 (63 per treatment group) participants will be required to complete at least Week 18 of the study.

The primary aim of this study is to estimate the relative bioavailability of the autoinjector compared with the SSD. Therefore, the sample size calculation for this study is based on the number of participants needed to achieve an acceptable level of precision in the estimate of relative bioavailability.

The variability of depemokimab PK parameters (AUC and Cmax) was informed by the depemokimab FTIH Study 205722 [GSK Document Number 2019N411063_00] and the mepolizumab Phase 1 Study 204958 [GSK Document Number 2017N342446_01], and is in line with results reported for monoclonal antibodies against soluble targets delivered subcutaneously.

Between CV_b of 30% was assumed for both AUC(0-inf) and Cmax. Based on this CV_b, with a sample size of 63 participants per treatment group, the 90% CI for an estimated ratio of autoinjector versus SSD of 1.00 will be (0.92, 1.09).

In addition, assuming a within-subject correlation of 0.8 between AUC and Cmax, and a true ratio of 1, a sample size of 63 participants will also provide 90% power to observe geometric CI of geometric mean ratio within the bioequivalence range of (0.8, 1.25) for both parameters.

Approximately 140 healthy participants will be enrolled (accounting for drop-out rate of 10% until Week 18) resulting in at least 126 evaluable participants (approximately 63 for each treatment group, 21 per injection anatomical site within each treatment group).

9.5.1. Sample Size Sensitivity

The table below provides the expected 90% CI estimates for a range of CV_b, assuming 5% difference in either direction in the ratio between autoinjector and SSD and n = 63 per treatment group.

CV_b	SDlogs	Estimated Ratio (Autoinjector/pre-filled safety syringe)	Expected Two-sided 90% CI
0.30	0.293	0.95	(0.87,1.04)
		1.00	(0.92,1.09)
		1.05	(0.96,1.15)
0.35	0.339	0.95	(0.86,1.05)
		1.00	(0.90,1.11)
		1.05	(0.95,1.16)

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 International Ethical Guidelines
    - Applicable ICH GCP guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, IDFU, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

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 or her representative will explain the nature of the study, including the risk and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protect 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.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about depemokimab or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the depemokimab approved for medical use or approved for payment coverage.

10.1.4. Data Protection

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

10.1.5. Committees Structure

Not applicable.

10.1.6. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the QTL plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and

requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite 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).
- 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 CSR/ equivalent summary unless local regulations or institutional policies require a different 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.
- 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 and its origin can be found in Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

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

10.1.10. Publication Policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- Hematology, clinical chemistry, urinalysis, and additional parameters to be tested are listed in Table 5. The tests detailed in Table 5 will be performed by a 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 5 Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	Red blood cell Indices: Mean corpuscular volume Mean corpuscular hemoglobin %Reticulocytes		White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]	Blood urea nitrogen	Potassium	AST	Total and direct bilirubin
	Creatinine	Sodium	ALT	Total protein
	Glucose	Calcium	Alkaline phosphatase[2]	Albumin
			Gamma-glutamyl transferase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones by dipstick • Microscopic examination and urinary albumin-creatinine ratio (if blood or protein is abnormal; evidence of microalbuminuria or hematuria of ≥1+)			
Pregnancy testing	• Highly sensitive serum pregnancy test at screening, for last follow-up visit (only WOCBP participants) and study exit/early termination; highly sensitive urine pregnancy test for other time points specified in SoA.			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) • Parasite screening (only required in regions with high risk or for participants who have visited high risk regions in the past 6 months). Sites should use local laboratories for this test, if needed • COVID-19 screening as required by clinic guidelines or local government requirements (all participants)			

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 Section 10.5 All events of ALT ≥3 × upper limit of normal (ULN) and total 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 to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination.).

- 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. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.
- **The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or**
- **The investigator considers that there is a reasonable possibility that the event was related to the administration of the study intervention**

10.3.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires in-patient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or INR >1.5 must be reported as SAE

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Recording, Assessment and Follow-up of AE and SAE

10.3.3.1. AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.3.2. Assessment of Intensity

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

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3.3.3. Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes 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 their 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.

10.3.3.4. Assessment of Outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.3.5. Follow-up of AE and SAEs

- 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 postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.3.6. Updating of SAE Information After Removal of Write Access to the Participant's ECRF

When additional SAE information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.3.3.7. Reporting of SAEs to GSK

SAE Reporting to SAE to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline 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 offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

SAE Reporting to GSK via Paper Data Collection Tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

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

10.4.1.2. Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):

a) Documented hysterectomy
b) Documented bilateral salpingectomy

c) Documented bilateral oophorectomy

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.
   - Females on HRT and whose menopausal status is in doubt will be excluded unless they agree to discontinue HRT to confirm their postmenopausal status.

10.4.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion / tubal ligation
Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable

Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction)

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

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT absolute</td><td>ALT ≥ 3 × ULN

If ALT≥ 3 × ULN AND total bilirubin[1,2] ≥ 2 × ULN (>35% direct bilirubin) or INR >1.5, report as an SAE.</td></tr>
<tr><th colspan="2">Required Actions, Monitoring 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 form, and complete SAE data collection tool if the event also meets the criteria for an SAE2
• Perform liver event follow-up assessments as described in the Follow-up Assessment column.
• Do not restart or rechallenge participant with study intervention
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING)
<u>MONITORING:</u>
If ALT ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN or INR >1.5
• Repeat liver chemistries (including ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within 24 hours
• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT ≥ 3 × ULN AND total bilirubin < 2 × ULN and INR ≤ 1.5:
• Repeat liver chemistries (including ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within 24-72 hours
• Monitor participants weekly until liver chemistries resolve, stabilize, or return to within baseline
</td><td>
• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample for PK analysis, within one week of meeting increased liver monitoring criteria
• Serum creatine phosphokinase and lactate dehydrogenase, gamma-glutamyl transferase, glutamate dehydrogenase, and serum albumin
• Fractionate bilirubin, if total bilirubin ≥2 × ULN
• Obtain complete blood count with differential to assess eosinophilia. Note: The mechanism of action of depemokimab leads to lowering of eosinophils
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications
• Record alcohol use on the liver event alcohol intake form
If ALT ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN or INR >1.5 obtain the following in addition to the assessments listed above:
• Antinuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT absolute	ALT ≥ 3 × ULN If ALT≥ 3 × ULN **AND** total bilirubin[1,2] ≥ 2 × ULN (>35% direct bilirubin) or INR >1.5, report as an SAE.

Required Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-up Assessments**
	• Serum acetaminophen adduct assay should be done (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g. where the participant has been resident in the clinical unit throughout). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease; complete Liver Imaging forms. • Liver biopsy may be considered and discussed with local specialists if available, for instance: o In patients when serology raises the possibility of AIH o In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In patients with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. 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 ≥ 3 × ULN and total bilirubin ≥ 2 × ULN (>35% direct bilirubin) or ALT ≥ 3 × ULN and INR >1.5, which may indicate severe liver injury (possible "Hy's Law"), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants
3. 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.

10.6. Appendix 6: Anaphylaxis Criteria ‘

Joint National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) Second Symposium on Anaphylaxis [Sampson, 2006]. The criteria do not make a distinction based on underlying mechanism. These criteria are summarized as follows:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
    a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    b) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    c) Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3) Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
    a) Adolescents (aged 12-17): low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure
    b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that participant’s baseline

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

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

10.7.1. Definition of Medical Device AE and ADE

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

10.7.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious AEs that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function.

• In-patient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. • Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious ADE that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of device deficiency

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

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

10.7.4.1. Medical Device AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK AE/SAE/device deficiency form.

- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
- If the site during the course of the study becomes aware of any serious, nonserious incident (including device deficiencies and malfunctions) related to any GSK non-IMP product they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.7.4.2. Assessment of Intensity

Refer to Section 10.3.3.2

10.7.4.3. Assessment of causality

Refer to Section 10.3.3.3

10.7.4.4. Follow-up of medical device AE/SAE and device deficiency

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

10.7.5. Reporting of Medical Device SAEs

Medical Device SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- 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 offline, then the site can report this information on a paper SAE form (see next table) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK device they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

Medical Device SAE Reporting to GSK via Paper Data Collection Tool

- Email/Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.

10.7.6. Reporting of SADEs

SADE Reporting to GSK

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

10.7.7. Reporting of Medical Device Deficiencies for Associated Person

- **Reporting to GSK**

If an Associated Person (i.e. e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the authorization to contact physician letter.

If follow-up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent.

- Medical device deficiencies that are not related to an AE or SAE should be reported via email to gsk-rd.complaints@gsk.com, using the medical device deficiency report form.
- If the medical device deficiency is related to a nonserious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to gsk-rd.complaints@gsk.com only.
- If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC.

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