Protocol Amendment

Study ID: 208021

Official Title of Study: An open-label, single dose study to investigate the pharmacokinetics, safety, tolerability, and immunogenicity of two dose levels of GSK3511294 administered subcutaneously in Chinese healthy participants

NCT ID: *NCT05140200*

Date of Document: 27-Apr-2021

TITLE PAGE

Protocol Title: An open-label, single dose study to investigate the pharmacokinetics, safety, tolerability and immunogenicity of two dose levels of GSK3511294 administered subcutaneously in Chinese healthy participants

Protocol Number: 208021/Amendment 01

Compound Number or Name: GSK3511294

Brief Title: Phase 1 study of GSK3511294 in healthy Chinese participants

Study Phase: Phase 1

Sponsor Name and Legal Registered Address:

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

Regulatory Agency Identifying Number(s): Not applicable

Medical Monitor Name and Contact Information

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

Approval Date: 27-APR-2021

SPONSOR SIGNATORY:

Protocol Title: An open-label, single dose study to investigate the pharmacokinetics, safety, tolerability and immunogenicity of two dose levels of GSK3511294 administered subcutaneously in Chinese healthy participants

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Jonathan Steinfeld
Sr. Clinical Development Director

Date

The signed page is a separate document.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY Dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 1	27-APR-2021	TMF-12466851
Original Protocol	19-OCT-2020	2020N437493_00

Amendment 1: 27-APR-2021

Overall Rationale for Amendment 1

This protocol amendment was created to make changes to the study fulfilling the request of China's Center for Drug Evaluation (CDE) to change investigational product (IP) supply of this study from Vial to pre-filled safety syringe (PFS), update some details related to COVID-19, add Radiation Risk Assessment according in line with GlaxoSmithKline (GSK) new standard operating procedure (SOP) and to correct typographical errors and inconsistencies. Protocol changes are described in the table below.

Section # and Name	Description of Change	Brief Rationale
Medical Monitor Name and Contact Information	Removed the Medical Monitor Name and Contact Information table in this protocol and stated the information will be provided in the Study Reference Manual (SRM) in the Title page	Avoid protocol amendments in case of personnel changes
Section 1.3: Schedule of Activities (SoA)	Correct the duration of monitoring local injection site reaction from 72 h to 8 h Updated the footnote related to chest X-ray screen (Footnote e) Removed the timepoint of Pharmacokinetic (PK) samples on Day 211 in Footnote h Added Anti- myeloperoxidase (MPO) antibody, anti- proteinase 3 (PR3) antibody, antinuclear antibodies (ANA), and anti-double stranded deoxyribonucleic acid (dsDNA) antibody tests at Pre-dose and a footnote (Footnote k) Added a footnote related to COVID-19 screening (Footnote l)	Align with study design and the Risk assessment Table Ensure Clarity and consistency across protocol Ensure consistency across the SoA, no PK sample will be taken on Day 211 Allow for evaluation of interval change for participants with suspected vasculitis Provide clarity about COVID-19 requirement at screening
Section 2.3.1: Risk Assessment	Added Radiation Risk Assessment due to the use of chest X-ray	Align with GSK SOP
Section 4.2: Scientific Rationale for Study Design	Added simulation result for the pharmacokinetics profile of a typical Chinese subject receiving GSK3511294	Provide rationale for the study period (26 weeks), which is shorter than the first time in humans (FTIH) study

Section # and Name	Description of Change	Brief Rationale
Section 5.2. Exclusion Criteria	Added a new exclusion criterion related to Alcohol/Substance Abuse (no. 6) Added a new exclusion criterion related to COVID-19 (no.7) Added a note related to COVID-19 vaccines in the Prior/Concomitant Medication criterion (no.8) Added a new exclusion criterion related to blood loss (no. 12) Moved the criteria related to alanine aminotransferase (ALT), bilirubin, QTc corrected by Fridericia's formula (QTcF) and abnormal chest X-Ray to the group of diagnostic assessments Added a note in exclusion criterion 16 to avoid recruitment of radiation worker or participants who have been exposed to ionising radiation in excess of 10 mSv above background over the previous three year period as a result of occupational exposure to radiation or as a result of research studies Updated COVID-19 diagnostic exclusion criterion (no.21)	Provide information related to Alcohol/Substance Abuse exclusion Provide information related to COVID-19 exclusion Provide information regarding use of the COVID-19 vaccines To prevent serial volunteers or blood donors from becoming anemic Put the information to the right place Align with GSK SOP Ensure Clarity and consistency across protocol
Section 6.1: Study Intervention(s) Administered	Change of IP)\ supply of this study from Vial to PFS Added information of injection device (Section 6.1.1)	Fulfill CDE's request Provide information related to injection device

Section # and Name	Description of Change	Brief Rationale
Section 6.9: Concomitant Therapy	Specified QT prolonging medications as Prohibited Medication Moved the Prohibited Medication criterion related to Recreational drug use to Section 6.9 Added a note related to COVID-19 vaccines to align with exclusion criterion no.8	Avoid QT prolong medications interference with QT-PK analysis Put the information to the right place Ensure consistency across Sections of the protocol
Section 8.3: Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting	Added Section 8.3.6 Medical Device Deficiencies	Provide safety information related to Medical Device Deficiencies
Section 9.2.1: Sample Size Assumptions	Added assessment of dropouts/missing data to minimize the risk of the potential impact of missing data and/or dropout	High dropout rate and missing data were expected due to the long terminal phase half-life ($T_{1/2}$) of GSK3511294
Section 9.4.1.2: Derived Plasma Pharmacokinetic Parameters	Added details of descriptive statistics and population PK parameters	High dropout rate and missing data were expected due to the long $T_{1/2}$ of GSK3511294. Population PK analysis may be used to overcome the missing data/drop out
Section 10.2. Appendix 2: Clinical Laboratory Tests	Updated the urinalysis related to the Microscopic examination and urinary albumin-creatinine ratio (UACR)	Align with global LA IL-5 SEA phase 3 study protocol

Section # and Name	Description of Change	Brief Rationale
Section 10: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS	Added Section 10.7 (Appendix 7) AEs, Adverse device effects (ADEs), SAEs, serious adverse device effects (SADEs), Unanticipated Serious Adverse device effects (USADEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies	Provide supporting information related to Medical Device

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 208021/01

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:			
Professional Qualification		Position	
Investigator Address:			
Investigator Phone Number:			
CRU address			
CRU phone number			
Investigator Signature			Date

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

GSK3511294 is a humanised monoclonal antibody (Immunoglobulin G1 [IgG1], kappa) antagonist of Interleukin (IL)-5 with an extended pharmacology. It blocks IL-5 binding to the IL-5 receptor complex causing a reduction in the circulating population of eosinophils. Two antagonists of IL-5, mepolizumab and reslizumab, are approved in countries outside of China in severe eosinophilic asthma, as an add-on treatment administered every 4weeks. GSK3511294 is expected to confer comparable efficacy and safety over a longer dosing interval. This single dose pharmacokinetic (PK) study will investigate the safety, tolerability, immunogenicity and PK of GSK3511294 100 mg and 300 mg, administered subcutaneously in Chinese healthy participants.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the plasma pharmacokinetics of single subcutaneous doses of GSK3511294 in Chinese healthy participants	• Plasma pharmacokinetic parameters of GSK3511294 after a single subcutaneous dose: AUC(0-∞), AUC(0-t), AUC(0-Week4), AUC(0-Week12), AUC(0-Week26), %AUCex, Cmax, tmax, tlast, CL/F, Vz/F, λz and t½ when assessable*
Secondary	
• To assess the safety and tolerability of single subcutaneous (SC) doses of GSK3511294 in Chinese healthy participants • To assess the immunogenicity of GSK3511294 in Chinese healthy participants	• Incidence of adverse events (AE), serious adverse events (SAE) • Change from baseline in laboratory safety data, at each post-dose timepoint during the 26 week treatment period, including hematology and clinical chemistry • Absolute values of C3 & C4 at each timepoint and the ratio to baseline at each post-dose timepoint during the 26 week treatment period • Change from baseline in vital signs, at each post-dose timepoint during the 26

Objectives	Endpoints
	week treatment period, including blood pressure, body temperature and pulse rate • Change from baseline in Electrocardiograms (ECG), at each post-dose timepoint during the 26 week treatment period • Frequency and titres of binding anti-drug antibodies (ADAs) to GSK3511294, before and after GSK3511294 administration.

* PK parameter abbreviations: AUC(0-∞) = area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; AUC(0-t) = area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments; AUC(0-WeekN) = area under the concentration-time curve from time zero to WeekN; %AUCex = percentage of AUC(0-∞) obtained by extrapolation; Cmax = maximum observed concentration; tmax=time of occurrence of Cmax; tlast = time of last quantifiable concentration; CL/F = apparent clearance following subcutaneous dosing; Vz/F = apparent volume of distribution after subcutaneous administration; λz= terminal elimination rate constant; t½ = terminal phase half-life.

The definition of applicable intercurrent events and corresponding strategy will be presented in Reporting and Analysis Plan (RAP).

Overall Design:

This is a single-centre, single dose, open-label study to evaluate the pharmacokinetics, safety, tolerability and immunogenicity of subcutaneously administered GSK3511294 100 mg and 300 mg in Chinese healthy participants.

Number of Participants:

20 (N=10 per dose level) Chinese healthy participants will be enrolled.

Treatment Arms and Duration:

All participants will receive a single dose of GSK3511294 subcutaneously of either 100 mg or 300 mg.

The 100 mg cohort (10 participants) will be initiated first.

The study team will review the safety data from the 10 participants in the 100 mg cohort before initiating 300mg cohort: at least 4-week safety data. In case of safety concerns, further investigation of the safety concerns will be conducted (including reviewing PK

data if deemed necessary) before initiating the 300 mg cohort. Criteria for Temporarily Delaying the start of the 300 mg cohort have been listed in Section 5.5.

Screening period (2 weeks):

All participants will attend the unit for screening within 14 days prior to their dosing date.

Study period (26 weeks)

Participants will be admitted the day before dosing, and all participants will remain in the clinical research unit (CRU) for approximately 8 hours after dosing for safety observation and other procedures. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, 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. Participants will be discharged only if the Investigator deems it safe for the participant to leave the unit.

Participants will return to the CRU for regular out-patient visits throughout the study according to Schedule of Activities.

Additional AE Follow up period (4 weeks):

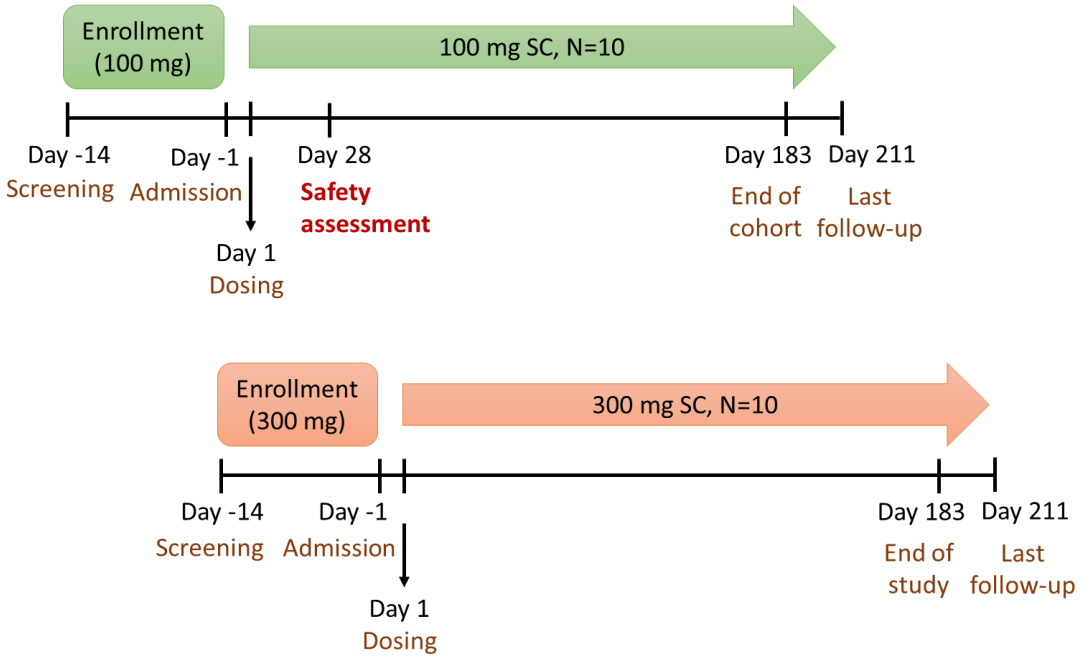
All participants will be telephoned for the additional AE follow up visit at Week 30 by investigators to further collect the safety information.

Total duration: The scheduled maximum study duration for each participant will be up to 32 weeks including up to 2 weeks screening period and 4 weeks AE follow up period.

Data Monitoring/ Other Committee: No

1.2. Schema

Figure 1 Study design



1.3. Schedule of Activities (SoA)

		In-Patient Period					Out-patient Visits											
		Day -1	Day 1				Day 2	Day 3	Day 5	W1 Day 8	W2 Day 15	W4 Day29	W8 Day57	W12 Day 85	W18 Day 127	W24 Day 169	Exit visit (W26) Day 183	Last follow up visit[i](W30) Day 211
Procedure	Screen[a]		Pre-dose	0h	2h	8h	24h	48h										
Informed consent	X																	
Inclusion & exclusion criteria	X	X	X															
Demography	X																	
Medical history[b]	X																	
HIV, HepB and HepC screen	X																	
Urine Drug Screen	X																	
FSH and estradiol[c]	X																	
Alcohol Breath Test		X																
Height, Weight and BMI[d]	X	X															X	
Full physical examination	X																X	
Brief physical examination		X			X			X		X			X					
Chest X-Ray[e]	X																	
12-lead ECG[f]	X	X	X		X	X	X	X	X	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	

		In-Patient Period					Out-patient Visits											
		Day -1	Day 1				Day 2	Day 3	Day 5	W1 Day 8	W2 Day 15	W4 Day29	W8 Day57	W12 Day 85	W18 Day 127	W24 Day 169	Exit visit (W26) Day 183	Last follow up visit[i](W30) Day 211
Procedure	Screen[a]		Pre-dose	0h	2h	8h	24h	48h										
Clin. Chem. and Urinalysis, Complement (C3 & C4)	X	X								X		X	X	X		X	X	
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody [k]			X															
Haematology (including blood eosinophil count)	X	X					X	X	X	X	X	X	X	X	X	X	X	
Parasite screening	X																	
COVID-19 screening	X[l]																	
PK blood samples[h]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity			X									X		X			X	
Concomitant medication	←----------													----------→				
AE/SAE review (inc local ISR up to 8 h after dosing)	X[j]	X[j]	X[j]	←----------													----------→	
Admission to unit		X																
Administer IP				X														
Discharge						X												

Abbreviations: AE = adverse event; ANA=antinuclear antibodies; BMI = body mass index; dsDNA = Double stranded Deoxyribonucleic acid; ECG = electrocardiogram; FSH = follicle stimulating hormone; h = hour(s); Hep B = Hepatitis B; Hep C = Hepatitis C; HIV= human immunodeficiency virus;;; IP = Investigational Product; ISR = injection site reactions; MPO=myeloperoxidase; PK = pharmacokinetic; PR3=proteinase 3; SAE = serious adverse event

Notes:

a. Screening up to 14 days before admission to unit. Screening procedures may be done at one or more out-patient visits, within the screening window.
b. Including cardiovascular (CV) disease, allergy history, alcohol and use of concomitant medication.
c. If required to confirm postmenopausal status.
d. Height at screen or Day-1 only.
e. Only applicable to the participants who haven't had an X-ray / Chest computed tomography (CT) scan within 6 months before screening.
f. Triplicate 12-lead ECG will be measured in supine position after 5 minutes rest at each time point.
g. Blood pressure and heart rate in triplicate before dosing; single measurements after dosing. Single temperature and respiratory rate measurements at all time points.
h. PK samples to be taken in all participants for GSK3511294 measurement at pre-dose (within 30 minutes prior to injection), 2h (±10 min), 8h (±10 min), Day2 (24h after dosing; ±15 min), Day3 (48h after dosing; ±30 min), Day5 (96h after dosing; ±30 min), Day8 (±1 day), Day 15 (±1 day), Day29 (±1 day), Day57 (±1 day), Day85 (±2 days), Day127 (±2 days), Day169 (±2 days) and Day 183 (±3 days)
i. Last follow up visit is followed up by phone call to collect AE/SAE.
j. Any SAEs assessed as related to study procedures or related to a GSK product will be recorded from the time a participant consents to participate in the study.
k. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
l. A COVID-19 test should be performed at screening and a further test is required within 72 hours prior to admission to the unit. Additional COVID-19 tests may be performed if clinically indicated or if needed to comply with institution and/or local government requirements.

- 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 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 Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

2.1. Study Rationale

This is a single dose study to investigate pharmacokinetics, safety, tolerability and immunogenicity of a single dose of GSK3511294 100 mg and 300 mg administered subcutaneously in Chinese healthy participants.

This Phase 1 study will be used together with data from the global first time in humans (FTIH) study and Phase 3 studies to support GSK3511294 development in China.

2.2. Background

Persistent eosinophil inflammation is a feature of more than 50% of patients with severe asthma [Chung, 2014]. Several monoclonal antibodies (mAbs) targeting eosinophil inflammation have received marketing authorization for asthma with an eosinophilic phenotype, including 3 targeting either interleukin-5 (IL-5) or its receptor (IL-5R): mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), and benralizumab (Fasenra). All three, 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 (HrQoL), 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 is provided by the well-characterized Ph3 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 in 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 this established efficacy and safety, 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].

GSK3511294 is a humanized, affinity matured mAb that blocks human IL-5 binding to its receptor and belongs to the established class of anti-IL-5 therapies for severe asthma management. Compared with mepolizumab, GSK3511294 contains 7 amino acid changes in the heavy chain sequence: 4 amino acid changes introduced in the heavy chain variable region, and 3 amino acid changes (YTE) introduced to the Fc region. The resulting antibody has increased affinity and half-life. Data indicate these amino acid changes extend the PK and pharmacology of GSK3511294 to allow less frequent dosing but are not predicted to alter the safety or efficacy profile of GSK3511294 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 LA anti-IL-5 therapy, GSK3511294 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 GSK3511294 administered subcutaneously in participants with mild-to-moderate asthma, who are controlled on low-medium daily dose of inhaled corticosteroids (ICS) and/or ICS/long-acting beta-2-agonists (LABAs), and short acting bronchodilators. Eligible participants had a screening blood eosinophil level of ≥200 cells/µL for relevance to the target population and facilitate investigation of the blood eosinophil profile following single doses of GSK3511294.

A detailed description of the chemistry, pharmacology and safety of GSK3511294 is provided in the current Investigator's Brochure (IB).

For more information, please refer to the GSK3511294 Investigator's Brochure (GSK Document Number 2016N295843_03. Section 5).

2.3. Benefit/Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK3511294 and 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 GSK3511294		
• 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 have been reported with GSK3511294 in FTIH study 205722 • In subjects with mild to moderate asthma. One subject reported an event under Hypersensitivity SMQ with preferred term of rash verbatim "localized rash both bends of arms", 82 days post 30 mg subcutaneous (SC) dose of GSK3511294. The event was non-serious, of mild intensity, resolved within 10 days and was considered unrelated to the study intervention by the investigator.	• Daily monitoring of serious adverse events (SAEs) by medical monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team. • Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 6). • Participants will be monitored in the clinical research unit (CRU) for immediate hypersensitivity and any other untoward effects for a minimum of 8 hours post-injection (at Day 1). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of GSK3511294, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the patient 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. • Participants will be discharged only if the Investigator deems it safe for the participant to leave the unit.

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 the 1-month toxicity study after administration of 10 mg/kg. A further monkey had a minimal focal inflammation after administration of 100 mg/kg. Immune complex disease was not observed in the 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 GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma (36 participants received GSK3511294; 12 participants received placebo).	• Participants with current diagnosis of vasculitis will be excluded. Participants with high clinical suspicion of vasculitis at screening will be evaluated and excluded from enrolment if diagnosed. • Daily monitoring of SAEs will be done by medical monitor/SAE coordinator; regular systematic review of adverse event (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 7.5)
• 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 GSK3511294 FTIH study 205722, injection site reactions were reported by one (3%) participant who received GSK3511294 and one (8%) participant who received placebo.	• Daily monitoring of SAEs by medical monitor/SAE coordinator; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or GSK safety review team.

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 vehicle control value) during Week 14. • In the GSK3511294 FTIH study (205722), a total of 2 participants had an elevated post-baseline QTcF value of potential clinical importance based on average from triplicate assessment: one on GSK3511294 100 mg SC (Week 2: 467 msec [all subsequent assessments were <450 msec and Day 1 pre-dose was 450 msec]) and one on placebo (Week 36: 455 msec [last assessment on study and Day 1 pre-dose was 414 msec]).	• ECGs will be performed according to timepoints specified in the SoA (Section 1.3) and the assessment will be done as specified in Section 8.2.3. • Participants with QTc prolongation on screening will be excluded (criterion 15, Section 5.2). • The detailed monitoring plan has been showed in Section 7.4.2. • Participants who will be enrolled in this study are healthy participants not expected to have a pre-existing clinically significant cardiac medical condition.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Risk of GSK3511294 affecting an unborn baby.	• Reproductive studies have not been conducted with GSK3511294; 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 the 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 pre-clinical reproductive toxicology studies of mepolizumab and reslizumab), a low genotoxic concern for mAbs in general, and a low transfer of monoclonal antibody (mAbs) into semen due to the inability of large molecular weight proteins such as GSK3511294 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.	• Only women of non child-bearing potential are eligible
Study Procedures		
• Potential risk for injury with phlebotomy.	• Risks with phlebotomy include bruising,	• Procedures to be performed by trained

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	bleeding, infection, nerve damage.	personnel (i.e., study nurse).
• Exposure to ionizing radiation from chest x-ray.	• To ensure participants are completely healthy and to comply with the local Chinese standard of care, participants who have not had a Chest x-ray/CT scan 6 months prior to the study will need to undergo a single Chest X-ray at screening. • The dose from a single chest X-ray should not exceed 20 microsieverts (μSv) and this corresponds to a lifetime risk of a fatal malignancy of about 1 in 1 million (International Commission on Radiological Protection [ICRP] 103), which falls into the 'trivial' risk category as defined by ICRP 62. The study will minimize exposure by using x-rays acquired as part of clinical care whenever possible.	• Only men and women of non-child bearing potential will be eligible for inclusion. Recruitment of participants who have been exposed to ionising radiation in excess of 10 mSv above background over the previous three year period as a result of occupational exposure or previous participation in research studies are excluded (criterion 16, Section 5.2). • Subjects are asked about any occupational exposure or previous participation in research studies at screening so that dose estimates can be obtained where necessary. • All procedures will be performed by a qualified technician

2.3.2. Benefit Assessment

No clinical benefit is expected for the healthy participants who are to be enrolled into this study.

This open-label, single dose PK study in healthy Chinese participants will provide initial pharmacokinetic, safety, tolerability and immunogenicity data in Chinese population, to evaluate the ethnic sensitivity in Chinese population versus overseas population.

Participants enrolled into this study are Chinese healthy participants. The participants' involvement will contribute to the understanding of the PK and safety profiles of GSK3511294 100mg and 300 mg administered SC in the Chinese population.

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 to be performed in 20 healthy participants is considered acceptable based on available data from FTIH study and risk mitigation strategy implemented for this protocol. The study provides the opportunity to generate PK, safety and tolerability information in Chinese population, thereby supporting subsequent dose justification for GSK3511294 in Chinese patients.

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the plasma pharmacokinetics of single subcutaneous doses of GSK3511294 in Chinese healthy participants	• Plasma pharmacokinetic parameters of GSK3511294 after a single subcutaneous dose: AUC(0-∞), AUC(0-t), AUC(0-Week4), AUC(0-Week12), AUC(0-Week26), %AUCex, Cmax, tmax, tlast, CL/F, Vz/F, λz and t½ when assessable*
Secondary	
• To assess the safety and tolerability of single subcutaneous (SC) doses of	• Incidence of adverse events (AE), serious adverse events (SAE)

Objectives	Endpoints
GSK3511294 in Chinese healthy participants • To assess the immunogenicity of GSK3511294 in Chinese healthy participants	• Change from baseline in laboratory safety data, at each post-dose timepoint during the 26 week treatment period, which including hematology and clinical chemistry • Absolute values of C3 & C4 at each timepoint and the ratio to baseline at each post-dose timepoint during the 26 week treatment period • Change from baseline in vital signs, at each post-dose timepoint during the 26 week treatment period, which including blood pressure, body temperature and pulse rate • Change from baseline in Electrocardiograms (ECG), at each post-dose timepoint during the 26 week treatment period • Frequency and titres of binding anti-drug antibodies (ADAs) to GSK3511294, before and after GSK3511294 administration.

* PK parameter abbreviations: AUC(0-∞) = area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; AUC(0-t) = area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments; AUC(0-WeekN) = area under the concentration-time curve from time zero to WeekN; %AUCex = percentage of AUC(0-∞) obtained by extrapolation; Cmax = maximum observed concentration; tmax=time of occurrence of Cmax; tlast = time of last quantifiable concentration; CL/F = apparent clearance following subcutaneous dosing; Vz/F = apparent volume of distribution after subcutaneous administration; λz= terminal elimination rate constant; t½ = terminal phase half-life.

The definition of applicable intercurrent events and corresponding strategy will be presented in Reporting and Analysis Plan (RAP).

4. STUDY DESIGN

4.1. Overall Design

This is a single-centre, single dose, open-label study to evaluate the pharmacokinetics, safety, tolerability and immunogenicity of subcutaneously administered GSK3511294 100 mg and 300 mg in Chinese healthy participants.

4.2. Scientific Rationale for Study Design

All participants will receive a single dose of GSK3511294 subcutaneously of either 100 mg or 300 mg.

The 100 mg cohort (10 participants) will be initiated first.

The study team will review the safety data from the 10 participants in the 100 mg cohort before initiating 300mg cohort: at least 4-week safety data. In case of safety concerns, further investigation of the safety concerns will be conducted (including reviewing PK data if deemed necessary) before initiating the 300 mg cohort. Criteria for Temporarily Delaying the start of the 300 mg cohort have been listed in Section 5.5.

Screening period (2 weeks):

All participants will attend the unit for screening within 14 days prior to their dosing date.

Study period (26 weeks)

Participants will be admitted the day before dosing, and all participants will remain in the CRU for approximately 8 hours after dosing for safety observation and other procedures. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, 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. Participants will be discharged only if the Investigator deems it safe for the participant to leave the unit.

Participants will return CRU for regular out-patient visits throughout the study according to Schedule of Activities.

To assess the potential exposure in Chinese subjects simulations were performed based on data from the FTIH study. Based on the assumption that body weight is the only impact factor on pharmacokinetics profile of GSK3511294, compared with a typical Caucasian subject of 70 kg, exposure in a typical Chinese subject of 60 kg for up to 183 days will cover 96% of overall exposure (AUC0-183d/AUC0-∞) for both 100 mg and 300 mg cohort. Even in the extreme case when a typical Chinese subject's clearance is only half of a Caucasian's, the exposure within 183 days will still cover 83% of overall exposure for both cohorts. In both cases, the coverage of exposure makes the

extrapolation of AUC valid. Hence, a study period of 26 weeks is deemed sufficient for assessing pharmacokinetics profile of GSK3511294 in Chinese.

Additional AE Follow up period (4 weeks):

All participants will be telephoned as the additional AE follow up visit at Week 30 by investigators to further collect the safety information.

Total duration: The scheduled maximum study duration for each participant will be up to 32 weeks including up to 2 weeks screening period and 4 weeks AE follow up period.

Data Monitoring/ Other Committee: No

4.3. Participant Input into Design

Not applicable.

4.4. Justification for Dose

GSK3511294 was investigated in a FTIH study (205722) outside of China over the dose range 2-300 mg SC. GSK3511294 was well tolerated up to a single SC dose of 300 mg and expected extended PK and pharmacology were demonstrated. Also, GSK3511294 is an antagonist of IL-5 that belongs to the same class as mepolizumab. Based on the pharmacology results of study 205722 and prior knowledge of mepolizumab pharmacology a dose of 100 mg SC administered every 26 weeks has been selected for investigation in the global Phase 3 clinical development program for severe asthma with an eosinophilic phenotype that is planning to enrol Chinese patients. Therefore a single SC dose of GSK3511294 100 mg is proposed to be investigated in this study to assess the PK and safety of GSK3511294 in the Chinese population. In addition a single SC dose of 300 mg is also proposed to be investigated in this study to provide further safety data above the 100 mg SC dose (the dose selected for the global Phase 3 clinical development program for severe asthma with an eosinophilic phenotype) CCI [redacted] CCI [redacted]

In study 205722 conducted in participants with mild/moderate asthma, overall linear PK was observed over the SC dose range 10 to 300 mg of GSK3511294, without evidence of target mediated disposition. This suggests that any difference in PK between Chinese and overseas populations due to the variability of target expression is considered unlikely. Slight difference in exposure between Chinese and overseas populations is possible, as body weight is a determinant of GSK3511294 exposure, similar to other mAbs. Approximately 12% higher exposure (AUC) is anticipated in Chinese participants compared with overseas participants given 100 mg and 300 mg fixed doses, considering 60 kg vs. 70 kg as the typical body weight in Chinese and overseas populations. In FTIH study 205722, GSK3511294 was well tolerated in patients with mild/moderate asthma receiving single SC doses up to 300 mg. The exposure (AUC) observed at 300 mg SC was 25-fold lower than the monkey exposure observed at the 100 mg /kg NOAEL dose, which supports the selection of a SC dose of 100 mg and 300 mg GSK3511294 for investigation in Chinese participants in this study. Furthermore, as an IgG1 monoclonal antibody, the elimination of GSK3511294 is via intracellular catabolism (proteolysis).

This clearance mechanism is non-specific and has large capacity. Reports of inter-ethnic differences in the non-specific pathways of protein elimination have not been identified and inter-ethnic differences in the catabolism of GSK3511294 are not anticipated, as was shown with mepolizumab.

In summary, GSK3511294 single SC doses of 100 mg and 300 mg are considered appropriate doses for investigation of the PK, tolerability and safety of GSK3511294 in Chinese healthy participants in this study in support of dose justification for Chinese patients with severe asthma with an eosinophilic phenotype[cci][redacted]

4.5. 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.

A participant is considered to have completed the study if he/she has completed all phases of the study including the exit visit at week 26.

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:

1. Age

Participant must be 18 to 45 years of age inclusive, at the time of signing the informed consent.

2. Type of Participant

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

3. Weight

Body weight ≥ 50.0kg for males, ≥ 45.0kg for females, and body mass index (BMI) within the range [19.0 – 26.0] kg/m2 (inclusive).

4. Sex and Contraceptive/Barrier Requirements

Male and female participants.

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

a. Male Participants: as GSK3511294 is a monoclonal antibody that is not anticipated to interact directly with Deoxyribonucleic acid (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 (see Appendix 4), not breastfeeding, and not a woman of childbearing potential as defined in Appendix 4.

5. Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of/significant history 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 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 (IgA) dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
3. Latent or chronic infections (e.g., genital herpes, urinary tract infections) or at risk if infection. Or opportunistic infection within 6 months prior to screening (e.g., a non-tuberculous mycobacterial infection or cytomegalovirus, pneumocystosis, aspergillosis).

4. Parasitic infection: Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening.
5. Vasculitis: Participants with current diagnosis of vasculitis. Participants with high clinical suspicion of vasculitis at screening will be evaluated and current vasculitis must be excluded prior to enrolment.
6. Alcohol/Substance Abuse: A history (or suspected history) of alcohol misuse or substance abuse
7. COVID-19:

   a-Participants with signs and symptoms suggestive of COVID-19 (i.e. fever, cough, etc) within 14 days of inpatient admission.

   b- Participants with known COVID-19 positive contacts in the past 14 days

Prior/Concomitant Medication

8. Use of prescription or non-prescription drugs, including vaccines, vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

   Note: Any approved COVID-19 vaccine by local government is permitted, but it should avoid being administered within 14 days of GSK3511294. If the vaccination within 14 days is unavoidable, then 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.

Prior/Concurrent Clinical Study Experience

9. The participant had participated in a clinical study or post-marketing study with an investigational or a non-investigational product during the previous 4 months or 5 half- lives (whichever is longer) preceding the administration of study medication of this study.
10. Exposure to more than 4 new chemical entities within 12 months prior to the dosing day.
11. The participant plans to concurrently participate in another clinical study or post-marketing study. Or have a treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing
12. Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56 day period.

Diagnostic assessments

13. ALT>1.5x ULN

14. Total bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%.
15. QTcF >450 msec.

    Notes:

    - The QTc is the QT interval corrected for heart rate, for the purposes of standardisation, QTc corrected by Fridericia's formula (QTcF) will be used across sites with central over-read to limit variability.
    - For purposes of data analysis, QTcF will be used as specified in RAP.
16. Abnormal chest X-Ray: A chest X-ray or CT scan that reveals evidence of clinically significant abnormalities. A chest X-ray must be taken at screen visit if a chest X-ray or CT scan is not available within 6 months prior to screen visit.

    Note: Participants should not be enrolled if the chest x-ray used in this study would cause exposure to ionising radiation in excess of 10 mSv above background over the previous three year period as a result of occupational exposure or previous participation in research studies (Clinically justified therapeutic or diagnostic exposures are not included in this cumulative calculation).
17. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screen or within 3 months prior to dose
18. A positive pre-study drug/alcohol screen
19. A positive test for HIV antibody.
20. A positive test for Parasite screening.
21. A positive test for COVID-19 at screening or during the period between screening and dosing of study drug.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Participants should fast for at least 8 hours before the screening visit and will be allowed to eat during the screening visit after blood draw for clinical chemistry has been completed. For other visits, fasting is not required.
- Participants will abstain from alcohol for 24 hours before the start of dosing period

5.3.2. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

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

5.5. Criteria for temporarily delaying initiation of the 300 mg cohort

If one or more of the following criteria are met, initiation of the 300 mg cohort will be temporarily delayed and all available safety data will be reviewed by the sponsor and investigator(s):

- one or more participants has:
    - a Serious Adverse Event (SAE) that is considered by the investigator to be possibly related to study drug
    - an episode of acute renal failure requiring renal replacement therapy that is at least possibly related to study drug
    - an episode of anaphylaxis that is considered by the investigator to be possibly related to study drug
    - an episode of angioedema that is considered by the investigator to be possibly related to study drug
    - a biopsy showing features of immune complex disease
    - 2 or more participants have severe Adverse Event (AEs) that is considered by the investigator to be possibly related to study drug

Participants who have been dosed before the time of the study delay will continue follow up visit in the study, as planned. Further participants may be dosed only if, after review, the sponsor and investigators consider it safe to do so.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

GSK3511294 is a humanised monoclonal antibody (IgG1, kappa) against recombinant human interleukin 5 (IL-5).

GSK3511294 liquid drug product will be supplied by GSK in a [redacted] The drug product and syringe will be assembled in a single use, disposable safety syringe to enable delivery of the drug product. Each device enables SC delivery of 100 mg GSK3511294 in [redacted]

The recommended storage condition is 2 - 8°C, protected from light. The expiry date, where required, is stated on the product label.

An overview of study intervention is provided in Table 1.

Table 1 Overview of Study Intervention

ARM Name	GSK3511294
Intervention Name	GSK3511294 Injection
Type	Biologic
Dose Formulation	Sterile liquid formulation in single use PFS
Unit Dose Strength(s)	100 mg/mL, [redacted]
Dosage Level(s)	100 or 300 mg (Day 1); 300 mg given as 3 separate injections given in the upper arm and separated by at least 5 cm.
Route of Administration	SC injection
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and Labelling	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.

PFS=Pre-filled safety syringe, IMP=Investigational Medicinal Product

6.1.1. Medical Devices

[redacted]

All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.6) and appropriately managed by GSK.

6.2. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.3. Preparation/Handling/Storage/Accountability

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

6.4. Measures to Minimize Bias: Randomization and Blinding

Not applicable, as this study is an open-label, single dose study.

6.5. Study Intervention Compliance

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

6.6. Dose Modification

There are no specific adjustment/stopping criteria for this study. Each participant will receive a single dose of GSK3511294 100mg or 300 mg subcutaneously in this study.

6.7. 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.

6.8. Treatment of Overdose

The dose of GSK3511294 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 Investigator's Brochure (GSK Document Number 2016N295843_03), single SC doses of GSK3511294 up to 300 mg were well tolerated by adult participants with mild/moderate asthma (6 participants received a 300 mg SC dose).

Each PFS 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:

- Contact the Medical Monitor immediately.
- Treat the patient with active supportive care as dictated by the subject's clinical status in the knowledge of the long half-life (approximately 41 days) of GSK3511294.
- Closely monitor the participant for AE/SAE and laboratory abnormalities for 30 weeks following the last administered dose.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

6.9. 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) before the start of 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 subject safety.

Recreational drug use and QT prolonging medications are not allowed throughout the study.

Paracetamol (acetaminophen) ≤2g/day as a mild analgesic is allowed throughout the study.

Any concomitant medication (eg. Vaccines) may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required. (Note: Any approved COVID-19 vaccine by local government is permitted, but it should avoid to be administered within 14 days of GSK3511294. If the vaccination within 14 days is unavoidable, then 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 enrolment 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

7.1. Discontinuation of Study Intervention

There is no specific discontinuation of study intervention criteria for this study. Each participant will receive a single dose of GSK3511294 100mg or 300 mg subcutaneously in this study.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or compliance reasons. This is expected to be uncommon.
- Participants are strongly encouraged to remain in the study for the entire duration but may prematurely withdraw from the study at any time at his/her own request, at the request of their legally authorized representative (LAR), or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- Participants who prematurely withdraw from the study should attend:
    - a Withdraw from Study (WS) Visit, 26 weeks after the administered dose of study intervention AND
    - a Follow-up visit/call, 30 weeks after the administered dose of study intervention for AE/SAE.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

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

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

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

Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

7.4. Criteria for increased monitoring of individual participants

7.4.1. Liver chemistry

Liver chemistry increased monitoring criteria and required actions and follow-up assessments have been designed to assure participant safety and evaluate liver event aetiology. Since this is a single dose study liver chemistry stopping criteria do not apply. If the following criteria are met increased liver chemistry monitoring is required:

- ALT≥3xULN
- ALT≥3xULN AND bilirubin ≥2xULN (>35% direct bilirubin) or (International

Normalized Ratio) INR >1.5

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

7.4.2. QTc

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 GSK medical monitor will be triggered in the following scenarios:

Refer for hospital admission & cardiology consult

- Arrhythmia or evidence of clinical impact e.g. syncope.

Direct observation for 24 hours before discharge with 48 h ambulatory Holter monitor and subsequent repeat assessment at 48 h*.

- 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.

* If QTcF (or QT if > 600 msec) remains the same/increases on assessment at 24 h (end of direct observation) and 72 h periods (after 48 h Holter monitor), then remain the observation and consideration of cardiology consult.

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

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

Owing to the adverse findings of arterial inflammation that were observed in the 1-month, but not at the 6-month, nonclinical 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 haematology, clinical chemistry and urinalysis.

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

- persistent* fever (*where persistent is considered to be a duration of ≥ 2 days)
- persistent* muscle and joint pain
- persistent* rash
- persistent* fatigue
- symptoms of peripheral neuropathy, like numbness or weakness
- laboratory abnormalities, e.g., decreased platelets, elevated creatinine, decrease in complement C3/C4, abnormal urinary albumin/creatinine ratio

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 to 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 indeed 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 GSK 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, anti-neutrophil cytoplasmic antibodies [ANCA]) in the setting of clinical concern regarding the possibility of immune complex disease. If necessary, testing for biomarkers, e.g., ANA, ANCA (anti-myeloperoxidase [MPO] antibody and anti-proteinase 3 [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 8.7). 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.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- 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. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 1.3.). 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 any extra assessments that may be required, will not exceed 70 mL.

8.1. Efficacy Assessments

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

8.2. Safety Assessments

- Planned time points for all safety assessments are provided in the SoA (Section 1.3). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety testes) may be added during the course of the study based on newly available data to ensure appropriated safety monitoring.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Oral or skin temperature, systolic and diastolic blood pressure, pulse and respiratory rate will be assessed.
- Blood pressure and pulse measurements will be assessed in the resting state with a completely automated device. Manual techniques will be used only if an automated device is not available.
- 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 heart rate will be measured in triplicate before dosing; single measurements after dosing. Single temperature and respiratory rate measurements will be measured at all time points.

8.2.3. Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and [QTc] intervals. ECG will be measured in supine position after 5 minutes rest.

8.2.4. Clinical Safety Laboratory Assessments

- All protocol required safety laboratory assessments will be conducted in CRU's laboratory. See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. The preparation and shipment of samples will follow CRU guideline. 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. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all the 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.

8.3.1. 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 the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Only women of non-childbearing potential are eligible for this study, so pregnancies are not expected. However, if a pregnancy does occur then: details of all pregnancies in females will be collected after the start of dosing and until 30 weeks after the dose.
- 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, fatal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.3.6. Medical Device Deficiencies

Medical devices (PFS) are being provided for use in this study as a delivery method for GSK3511294 injections. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Section 10.7.

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

8.3.6.1. Time Period for Detecting Medical Device Deficiencies

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

8.3.6.2. Follow-up of Medical Device Deficiencies

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

8.3.6.3. Prompt Reporting of Medical Device Deficiencies to 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 utilised.
- The Sponsor will be the contact for the receipt of device deficiency reports.

8.3.6.4. Regulatory Reporting Requirements for Medical Device Incidents

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

8.4. Pharmacokinetics

8.4.1. Blood Sample Collection

Blood samples for determination of GSK3511294 plasma concentrations will be collected at the time points indicated in the Schedule of Activities table (Section 1.3). Each PK sample must be collected as close as possible to the planned time relative to the dose (which is 0 h) administered to the participant on day 1. The actual date and time of each blood sample collection will be recorded into CRF.

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

8.4.2. Sample Analysis

Samples analysis will be performed under the control of Bioanalysis, Immunogenicity & Biomarkers (BIB), GlaxoSmithKline. Concentrations of GSK3511294 will be determined in plasma samples using a validated bioanalytical method.

8.5. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Blood samples for detection of anti-GSK3511294 antibodies will be collected at the time-points specified in the SoA (Section 1.3). The actual date and time of each blood sample collection will be recorded. Details for immunogenicity blood sample collection, processing, storage, and shipping will be provided in the SRM.

Samples analysis will be performed under control of BIB, GlaxoSmithKline. The presence of anti-GSK3511294 antibodies will be determined in serum samples using a validated bioanalytical method, with a tiered analyses approach using a screening assay, confirmation assay and titre assay. If necessary, further immune response characterization may be performed as needed.

8.8. Health Economics OR Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of this study is to evaluate the pharmacokinetics of GSK3511294 100mg and 300mg administered subcutaneously. There are no formal hypothesis tests associated with this objective and no formal significance tests.

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

There are no formal calculations of power or sample size for this study. The sample size of approximately 10 participants per cohort will be enrolled into the study to obtain at least 6 participants per cohort with at least 18-week PK data has been chosen based on feasibility.

Any impact of missing data and/or dropout will be assessed during the study. Specifically, in each cohort, if there are less than 6 participants with at least 18-week PK data, a maximum of up to 6 additional participants will be recruited in order to target at least 6 participants with at least 18 week PK data. In the case when there are less than 6 participants with at least 18-week PK data available in each cohort after the recruitment of additional participants, population PK analysis will be used to overcome the potential impact of missing data and/or dropout.

For each cohort, with 6 participants with at least 18-week PK data, assuming that the coefficients of variation% (CV%) of Cmax and AUC(0-∞) is 25.4% and 28.5% respectively (from global FTIH study, GSK Document Number 2019N411063_00), it is estimated that the lower and upper bounds of the 95% confidence interval (CI) would lie within 30.0% of the point estimate for Cmax and 34.1% of the point estimate for AUC(0-∞).

9.2.2. Sample Size Sensitivity

Different participant numbers with at least 18-week PK data and the corresponding precisions of Cmax and AUC(0-∞) are provided in the Table 2 below. It assumes the CV% of Cmax and AUC(0-∞) is 25.4% and 28.5% respectively.

Table 2 Different Participant Numbers and Corresponding Precisions

Pharmacokinetic parameter	Participant number with at least 18-week PK data	Precision (Half width of 95% confidence interval)
Cmax	6	30.0%
	7	26.0%
	8	23.2%
	9	21.2%
	10	19.6%
AUC(0-∞)	6	34.1%
	7	29.5%
	8	26.3%
	9	24.0%
	10	22.1%

9.2.3. Sample Size Re-estimation

No sample size re-estimation will be performed.

9.3. Analysis Populations

For purposes of analysis, the following populations are defined:

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

9.4. Statistical Analyses

Reporting and analysis plan (RAP) will be finalized prior to Database Release (DBR) and it 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 most important endpoints including primary and key secondary endpoints. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and clinical study report.

9.4.1. Primary Endpoint(s)

All pharmacokinetic analyses will be conducted on the Pharmacokinetic Population.

9.4.1.1. Raw Plasma PK Concentrations

Plasma concentrations of GSK3511294 will be listed and summary statistics, including arithmetic mean, median, standard deviations, geometric mean and coefficient of variation per GSK Integrated Data Standards Library (IDSL) standard, will be summarised by dose and nominal time. Individual concentration-time profiles and median/mean profiles by GSK3511294 dose will be plotted on both linear and semi-logarithmic scale.

9.4.1.2. Derived Plasma Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, GSK. Plasma concentration-time data for GSK3511294 will be analysed by non-compartmental methods according to GlaxoSmithKline guidance document, GUI_00000051487 and using Phoenix WinNonlin.

Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit, for each dose of GSK3511294 and for each participant:

- Cmax
- tmax
- AUC(0-t), AUC(0-week4), AUC(0-week12) AUC(0-week26) and AUC(0-∞)
- %AUCextrapolated
- tlast
- CL/F
- Vz/F
- λz
- the number of points used to determine λz
- t1/2

For each of the derived serum GSK3511294 pharmacokinetic parameters, the following summary statistics will be calculated: median, minimum, maximum, arithmetic mean, standard deviation, coefficient of variation, geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data.

In the case when there are less than 6 participants with at least 18-week PK data available in each cohort after the recruitment of additional participants, population PK analysis will be used to account for the potential impact of missing data and/or dropout data. Descriptive statistics (mean, standard deviation, 95% CI , minimum, median, maximum, geometric mean and CV%) will be used to summarize the population PK parameters: CL, bioavailability (F), absorption rate constant (ka) and AUC(0-∞).

Pharmacokinetic data will be presented in graphical and/or tabular form and will be listed and summarized descriptively by dose group.

All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, Research and Development (R&D).

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Biostatistics, GlaxoSmithKline.

9.4.2. Secondary Endpoint(s)

Full details of safety data analyses in the safety population will be presented in the Reporting and Analysis Plan (RAP).

Summaries of safety data will include adverse events, serious adverse events, vital signs, ECG, and laboratory data. Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

The positive rate of anti-drug antibodies (ADAs) to GSK3511294 before and after GSK3511294 administration will be summarized and listed based on the safety population. Details will be presented in RAP.

9.5. Interim Analysis

No formal interim analysis is planned for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, 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/her representative will explain the nature of the study 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, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

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 GSK3511294 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the GSK3511294 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. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients' received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as

Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Study and Site Start and Closure

First Act of Recruitment

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

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally

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

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

10.2. Appendix 2: Clinical Laboratory Tests

- Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 3. The tests detailed in Table 3 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 3 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose 8 hours fasted at screening	Calcium	Alkaline phosphatase[2] Gamma-Glutamyl Transferase (GGT)	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination and urinary albumin-creatinine ratio (UACR) (if blood or protein is abnormal [evidence of microalbuminuria or haematuria of ≥1+])			

Laboratory Assessments	Parameters
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • HIV antibody, hepatitis B surface antigen HBsAg, and hepatitis C virus antibody) • Parasite Screening (all participants) • COVID-19 Screening as required by CRU or local government (all participants)

NOTES :

1. 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.

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • [If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.] • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

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

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Definitions
Woman of Childbearing Potential

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

Women in the following categories are not considered to be Woman of Childbearing Potential

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

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

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be excluded unless they agree to discontinue HRT to confirm their postmenopausal status

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

Liver chemistry increased monitoring criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT≥3xULN If ALT≥3xULN **AND** total bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) OR international normalized ratio (INR)>1.5, Report to GSK as an SAE.

Required Actions, Monitoring and Follow up Assessments	
Actions	**Follow Up Assessments**
• Report the event to GSK **within 24 hours** • Complete the liver event form, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver chemistry event follow up assessments as described in the Follow Up Assessment column. • Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING**) **MONITORING:** **If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended	• Viral hepatitis serology[3] • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, obtained within a week of meeting increased liver monitoring criteria[4] • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin. • Fractionate bilirubin, if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia. Note: The mechanism of action of GSK3511294 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 CRF page including acetaminophen, herbal remedies, recreational drugs and other over the counter medications.

If ALT≥3xULN AND total bilirubin < 2xULN and INR ≤1.5: • Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	• Record alcohol use on the liver event alcohol intake form **If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5** obtain the following in addition to the assessments listed above: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (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 computerised tomography) to evaluate liver disease; complete liver imaging form. • Liver biopsy may be considered and discussed with local specialists if available for instance: o In patients when serology raises the possibility of autoimmune hepatitis (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. if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported to GSK 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 Immunoglobulin M (IgM) antibody; HbsAg and HBcAb; hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to pk blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in

the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

10.5.1. References

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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 summarised as follows:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised 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 PEF, hypoxemia)
    b) Reduced blood pressure (BP) 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 patient (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 PEF, hypoxemia)
    c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a) Adolescents (aged 12-17): low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

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10.7. Appendix 7: AEs, Adverse device effects (ADEs), SAEs, Serious Adverse device effects (SADEs), Unanticipated Serious Adverse device effects (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 European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the Sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.7.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An 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 unfavourable 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. • An ADE is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event that:
a. Led to death
• Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term ‘life-threatening' in the definition of ‘serious' refers to an event in which the participant was at risk of death at the

time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalisation. Planned hospitalisation 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.
c. Led to foetal distress, foetal 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 adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • 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.
USADE definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of Device Deficiency

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

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

AE, SAE and Device Deficiency Recording

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

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

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

Assessment of Causality

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

Follow-up of AE/SAE/device deficiency

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

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

10.7.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator.
- In rare circumstances and in the absence of 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.
- Contacts for SAE reporting can be found in the SRM.

10.7.6. Reporting of SADEs

SADE Reporting to GSK

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify

appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in the Study Reference Manual (SRM).

10.8. Appendix 8: Abbreviations and Trademarks

Abbreviations

µSv	Microsieverts
ADA	Anti-drug antibody
ADE	Adverse device effect
AE	Adverse Event
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
%AUCex	Percentage of AUC(0-∞) obtained by extrapolation
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments
AUC(0-Week x)	Area under the concentration-time curve from time zero to Week x
Anti-HBc	Hepatitis B core Antibody
BIB	Bioanalysis, Immunogenicity & Biomarkers
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CDE	China's Center for Drug Evaluation
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance following subcutaneous dosing
Cm	Centimeter
Cmax	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling and Simulation
CRF	Case Report Form
CRP	C-reactive protein
CRU	Clinical Research Unit
CT	Computed tomography
CV%	Coefficients of variation%
CV	Cardiovascular
DNA	Deoxyribonucleic acid
dsDNA	Double stranded deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid

ESR	Erythrocyte sedimentation rate
F	bioavailability
FAAN	Food Allergy and Anaphylaxis Network
FSH	Follicle stimulating hormone
FTIH	First Time in Humans
G	Grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma-glutamyl transferase
GINA	Global Initiative for Asthma
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline
H	Hours
HBsAg	Hepatitis B Surface Antigen
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICRP	International Commission on Radiological Protection
ICS	Inhaled corticosteroid
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
IFU	Instruction for use
Ig	Immunoglobulin
IgG1	Immunoglobulin G1
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ISR	Injection site reactions
ka	Absorption rate constant
kDa	Kilodalton
Kg	Kilogram
L	Litre
LABA	Long acting β-agonist
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume

MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
mm Hg	Millimetre of mercury
Mol	Mole
MPO	Myeloperoxidase
MSDS	Material Safety Data Sheet
msec	Milliseconds
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Disease
NOAEL	No Observed Adverse Effect Level
PR3	Proteinase 3
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEF	Peak expiratory flow
PFS	Pre-filled safety syringe
pH	Hydrogen ion concentration
PK	Pharmacokinetics
PTS	Platform Technology and Science
QC	Quality control
QTcF	QTc corrected by Fridericia's formula
R&D	Research and Development
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
SADE	Serious Adverse device effect
SAE	Serious Adverse Event
SC	Subcutaneous
SGPT	Serum glutamic pyruvic transaminase
SGOT	Serum glutamic oxaloacetic transaminase
SOP	Standard operating procedure
SRM	Study Reference Manual
T	Time of last observed quantifiable concentration
t½	Terminal phase half-life
Tlast	Time of last quantifiable concentration
Tmax	Time of occurrence of Cmax
TNF-α	Tumour necrosis factor-alpha
TTS	Study Specific Technical Terms of Supply Agreement/Memo
UACR	Urinary albumin-creatinine ratio
UK	United Kingdom
ULN	Upper Limit of Normal
USADE	Unanticipated Serious Adverse device effect
Vz/F	Apparent volume of distribution after subcutaneous

	Administration
WBC	White blood cell
W/V	Weight/volume
µL	Microlitre

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