TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A randomised double-blind (sponsor open), placebo controlled, single ascending dose, First Time in Human study in participants with mild to moderate asthma to assess safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of GSK3511294 administered subcutaneously.

Compound Number: GSK3511294

Development Phase: I

Effective Date: 07-JAN-2019

Protocol Amendment Number: 06

Author (s): PPD
PPD
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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N270529_00	2017-JUN-13	Original
2016N270529_01	2017-JUN-21	Amendment No. 1
To correct errors in the Secondary Medical Monitor's email address and in the inflammatory marker tests to be performed at screening.		
2016N270529_02	2017-AUG-04	Amendment No. 2
To amend the pharmacokinetic stopping criterion and clarify that saline for placebo will be an EU licensed product sourced locally by trial sites, in response to comments from the Medicines and Healthcare Products Regulatory Agency.		
2016N270529_03	2017-SEP-04	Amendment No. 3
To correct errors and make minor clarifications.		
2016N270529_04	2018-FEB-02	Amendment No. 4
To amend the timeframe for collection of PEF measurements. To clarify that demography, height, weight and BMI will be collected at the pre-screening visit if this visit is required. Alignment of ECG collection timeframe. Clarify timeframe for review of safety data from sentinel participants. Clarify that sentinel participants will be used at each escalating dose level. To remove the necessity for evidence of airway hyperresponsiveness, airflow variation (peak flow rate or FEV_1) or reversible airflow obstruction at inclusion. Added live vaccines to prohibited concomitant medications list. Added Right Bundle Branch Block as an exclusion criteria. Clarification of the study halting criteria. Clarification that each participants consent must be available, as well as obtained, before they are entered into the study. Added an exclusion criteria regarding vulnerable participants. Clarify the definition of a pre-screening failure. Added in country specific requirements for Germany, concerning the addition of Hepatitis B core antibody test screening and to increase the in-patient period to 8-days post dosing. Clarified that the PK sample information is located in the appropriate lab manual and not the study reference manual. To ensure there is no un-blinding that can occur for Eosinophil counts due to availability of other components and their contributions to WBC count.		

GlaxoSmithKline Document Number	**Date**	**Version**
2016N270529_05	2018-JUN-18	Amendment No. 5
A raw QT interval change from baseline as one of the criteria for limiting dose escalation and for increased monitoring of individual participants has been included in error. QTcF has been chosen as the most appropriate corrective measure of QT for this study and this is now reflected throughout. Accordingly, one of the required criteria for limiting further dose escalation and increased monitoring of individuals is now a change in QTcF from baseline of > 60 msec. To remove the requirement for reversibility testing at pre-screening/screening, as evidence of reversibility is no longer a requirement for inclusion as per the previous amendment. Consequently, participants who would not be a screen failure under the entry criteria in the current version of the protocol may be rescreened. Furthermore, participants that were not a screen failure but could not be dosed during the screening window due to logistical reasons may also be rescreened. To extend the PK sampling period in the 2 mg and 10 mg cohorts, to better characterise the PK profile of GSK3511294. To clarify that local labs are required for all sentinel participants at the 48 hour time point to enable dosing of the rest of the cohort. As the German in-patient stay is longer than the UK, local labs prior to discharge from the clinical site are required on Day 8 and not at 48 hours post dosing (Day 3). Minor corrections of typos throughout.		
2016N270529_06	2019-JAN-07	Amendment No. 6
Inclusion of additional interim analyses to better assess blood eosinophil count return towards baseline profiles at the highest dose levels investigated and better inform dose and dosing regimen to move forward into the next phase of development. The earliest additional interim analysis is planned no earlier than once data is available at the 26-week time point after dosing Cohort 4 (planned 100 mg dose).		

SPONSOR SIGNATORY

PPD

07 January 2019

Joanna Marks-Konczalik
Early Development Leader

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	PPD	PPD		GSK Gunnels Wood Road Stevenage Hertfordshire SG1 2NY UK
Secondary Medical Monitor	PPD	PPD	PPD		GSK Gunnels Wood Road Stevenage Hertfordshire SG1 2NY UK
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Sponsor Legal Registered Address:

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): 2016-004256-30

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number: 205722

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:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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1. PROTOCOL SYNOPSIS FOR STUDY 205722

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 severe eosinophilic asthma, as an add-on treatment administered every 4 weeks. GSK3511294 is expected to confer efficacy over a dosing interval of up to 6 months. This single ascending dose first time in humans (FTIH) study will investigate safety, tolerability, immunogenicity, pharmacokinetics (PK) and pharmacodynamics (PD) of GSK3511294, administered subcutaneously in participants with mild to moderate asthma maintained on a low–medium daily dose of inhaled corticosteroids (ICS) or ICS/long acting β-agonist (LABA), and short acting β-agonist (SABA). To facilitate the investigation of blood eosinophil counts following single doses of GSK3511294, eligible participants will have a blood eosinophil count of ≥ 200 cells/μL at screening. This should enable a quantification of the prolonged blood eosinophil reduction that is anticipated in humans resulting from the combination of the extended half-life and greater affinity to IL-5 of GSK3511294.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of ascending single subcutaneous (SC) doses of GSK3511294 in participants with mild to moderate asthma	• Adverse events (AE), serious adverse events (SAE), including systemic reactions and local injection site reactions • Vital signs, electrocardiograms (ECG), laboratory safety data – including liver and renal chemistry, high sensitivity C-reactive protein (hsCRP), and complement (C3 and C4)
Secondary	
• To evaluate the plasma pharmacokinetics of ascending single subcutaneous doses of GSK3511294 in participants with mild to moderate asthma	• Plasma pharmacokinetic parameters of GSK3511294 after single subcutaneous doses: AUC(0-∞), AUC(0-t), AUC(0-Week4), AUC(0-Week12), AUC(0-Week26), %AUCex, Cmax, tmax, tlast, CL/F, Vd/F, λz and t½ when assessable*

Objectives	Endpoints
• To evaluate the dose response of blood eosinophil counts after ascending single subcutaneous doses of GSK3511294 in participants with mild to moderate asthma	• Ratio to baseline in absolute blood eosinophil count
• To assess the immunogenicity of GSK3511294	• Frequency and titres of binding anti-drug antibodies (ADAs) to GSK3511294, before and after GSK3511294 administration

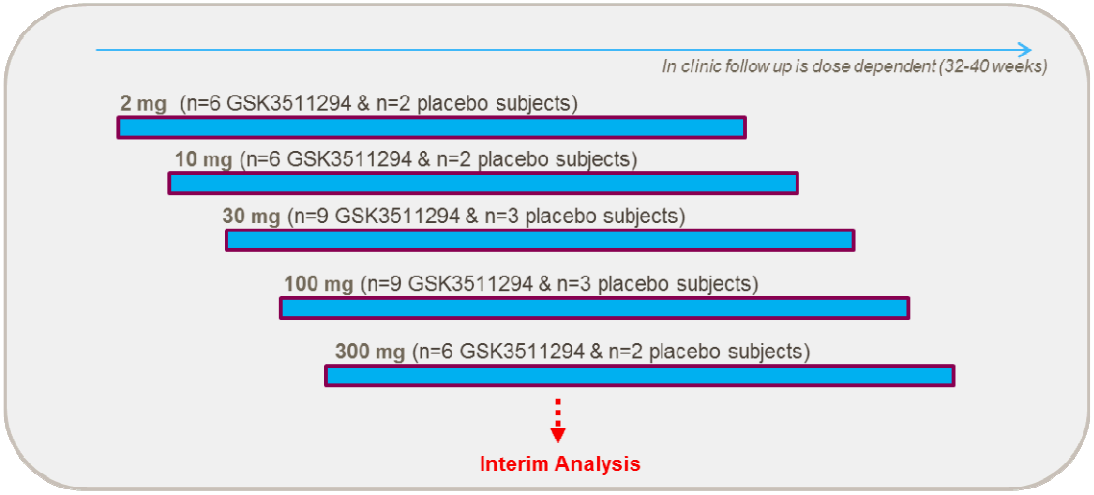
* PK parameter abbreviations: AUC(0-∞) = area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; AUC(0-t) = area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments; AUC(0-WeekN) = area under the concentration-time curve from time zero to Week N; %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; Vd/F = apparent volume of distribution after subcutaneous administration; λz = terminal elimination rate constant; t½ = terminal phase half-life.

Overall Design

This is a single ascending dose FTIH study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of subcutaneously administered GSK3511294 in participants with mild to moderate asthma and blood eosinophils ≥ 200 cells/μL.

This study is a multi-center, randomised, double-blind (sponsor clinical pharmacology modelling and simulation [CPMS] and statistician representatives open), placebo-controlled, parallel-group study. Each participant will receive a single dose of GSK3511294 or placebo, as shown in Figure 1.

Figure 1 Summary of GSK3511294 first-time-in-human study design



Notes: Planned single ascending SC doses of GSK3511294 are 2, 10, 30, 100 and 300 mg. Actual dose levels beyond the 2 mg starting dose will be confirmed based on the emerging data. Planned cohort sizes are shown; additional participants may be added to cohorts, if necessary to characterise the pharmacokinetics or pharmacodynamics of GSK3511294. In each cohort, participants will be randomised 3:1 to receive GSK3511294 or placebo. Additional cohorts of up to 12 participants may be added to test additional dose levels or to repeat a dose level already tested, if deemed necessary; however, the dose will not exceed 300 mg. The planned sample size is n=48 participants; the maximum sample size is n=72 participants (excluding replacements for prematurely withdrawn participants).

- Sentinel participants: In each cohort, one placebo and one GSK3511294 participant will be dosed before the remaining participants. Providing no safety issues are identified in the sentinel participants over an observation period of at least 72 hours, the remaining participants in the cohort may be dosed. The Investigator will discuss any safety concerns with the GlaxoSmithKline (GSK) medical monitor before dosing the remaining participants in a cohort. Sentinel dosing is not required in cohorts investigating a dose lower than or equal to the highest dose tested to date.

Treatment Arms and Duration

- Blood eosinophils pre-screen and screening: a blood eosinophils pre-screen assessment will be performed. Participants are eligible to skip the blood eosinophils pre-screening visit and go directly to the screening visit, if they have a documented blood test result within 12 weeks before dosing demonstrating a blood eosinophil level $\geq$ 200 cells/µL. Participants who fulfil the pre-screening criteria will then attend the clinic for a full screening visit. Blood eosinophil level will be measured at screening to confirm eligibility.
- In-patient period: Participants will be admitted the day before dosing, and the minimum post dose in-patient period for all participants will be 72 hours in the UK and 8 days in Germany (a longer in-patient stay is required in Germany to satisfy regulatory comments). Participants will be monitored for local injection site reactions and allergic reactions for at least 72 hours post dose. In the case of such reactions, appropriate medical treatment will be administered. Participants will be discharged only if the Investigator deems it safe for the participant to leave the unit.

- Follow up period: Participants will receive post-dose assessments during the in-patient period and attend the clinic for further post-dosing assessments. The follow-up period will be up to 40 weeks, and will be dose dependent, based on the predicted blood eosinophil profile. Participants in cohorts receiving 2 and 10 mg GSK3511294 will attend the clinic visits up to week 32, participants in cohorts receiving 30 mg and 100 mg will attend clinic visits up to week 36, and participants in cohorts receiving 300 mg will attend clinic visits up to week 40. (For unplanned dose levels, the duration of follow-up will be documented in a Note to File.) The follow-up period for any participant may be adjusted, if necessary, based on the anticipated duration of action or any safety concerns that may emerge during the study.
- Total duration: The scheduled maximum study duration for each participant who receives GSK3511294 or placebo will be up to 44 weeks (excluding pre-screening for blood eosinophils), including up to 28 days for screening, 4 days as an in-patient in the UK and 9 days in Germany, and up to 40 weeks post-dosing to investigate the PD; blood eosinophil count and safety profile.
- Dose escalation: The dose escalation committee (DEC), comprised of members from the GSK Study Team and the Investigator(s), will review available data from all participants in each cohort before initiating each new dose level. Dose escalation may occur only after review of the following data at the highest dose level tested to date: at least 4 weeks' post-dose safety data and at least 2 weeks' post-dose PK data from at least 4 participants on active treatment; and at least 72 hours' post-dose safety data from the remaining participants in the cohort. As the sponsor CPMS and statistician representatives will be unblinded, to minimise the risk of unblinding investigators and other sponsor representatives during DEC meetings, no individual PK or PD data will be discussed; only blinded summary statistics will be available to blinded DEC members.

Type and Number of Participants

The total number of participants pre-screened/screened will meet the need to randomise a sufficient number of participants to fulfil the study objectives. It is anticipated that after completion of successful screening, approximately 48 mild to moderate asthmatics, with blood eosinophils $\geq$ 200 cells/μL at screening, will be randomised. As the number of cohorts and number of participants per cohort are flexible, the protocol allows randomization of up to 72 participants (not including replacements for prematurely discontinued participants), split between about 6 clinical sites.

2. INTRODUCTION

2.1. Study Rationale

This is a single ascending dose FTIH study to investigate safety, tolerability, immunogenicity, PK and PD of GSK3511294, administered subcutaneously in participants with mild to moderate asthma, maintained on a low–medium daily dose of inhaled corticosteroids (ICS) or ICS/long acting β-agonist (LABA), and short acting β-agonist (SABA). Eligible participants will be required to have a blood eosinophil count of ≥ 200 cells/μL at screening, to facilitate investigation of reduction in blood eosinophil counts following single doses of GSK3511294, and to quantify the prolonged blood eosinophil reduction that is anticipated in humans given the expected extended half-life and greater IL-5 affinity of GSK3511294.

In stream data review will occur during the study to support dose escalation decisions, and formal interim analyses are planned to ensure accumulated safety, PK and PD data is deemed sufficient to determine the doses, and dosing interval, to take forward to the next phase of development.

2.2. Brief Background

Interleukin-5 (IL-5): IL-5 mediates the growth and differentiation of eosinophils in the bone marrow and also their recruitment and activation within tissues [Corren, 2012]. Eosinophils circulate in the blood with a half-life of 8 to 18 hours and can persist in tissues for longer (days to weeks) [Kovalszki, 2016]. Therefore, inhibiting IL-5 will remove a key eosinophil growth factor, and given the short half-life of eosinophils, will cause a rapid reduction in the circulating population. Reduction in eosinophils has been identified as a therapeutic strategy for numerous disorders, with monoclonal antibodies (mAbs) targeting IL-5, such as mepolizumab, currently approved in severe eosinophilic asthma and in development for other indications [Legrand, 2015].

GSK3511294: GSK3511294 is an extended pharmacology humanised monoclonal antibody (Immunoglobulin G1 [IgG1], kappa). It inhibits IL-5 signalling by blocking human IL-5 binding to the IL-5 receptor complex, which is expressed on the eosinophil cell surface. Treatment with anti IL-5 monoclonal antibodies (mepolizumab and reslizumab) administered every 4 weeks appears well tolerated, and is approved as an add-on maintenance treatment in patients with severe refractory eosinophilic asthma. GSK3511294 is anticipated to confer a similar efficacy and benefit:risk profile as other IL-5 targeting monoclonal antibodies, while being administered with a longer dosing interval.

GSK3511294 demonstrated an approximately 29-fold increase in IL-5 potency compared to mepolizumab in a cell based *in vitro* assay, and approximately 2-fold reduction in clearance in a single dose cynomolgus monkey pharmacokinetic (PK)/pharmacodynamic (PD) study. Consistent with the *in vitro* data, in cynomolgus monkey, GSK3511294 demonstrated an IL-5 binding affinity approximately 30-fold greater than mepolizumab, as evaluated by total IL-5 profile and duration of blood eosinophil suppression. Return to

50% of the maximal blood eosinophil suppression effect was observed at around Day 169 for GSK3511294 (1 mg/kg) and Day 29 for mepolizumab (1 mg/kg).

The safety profile of GSK3511294 (10 and 100 mg/kg doses) has been evaluated in a 4-week single dose and a 26-week repeat dose toxicity (2 doses 3 months apart given at Day-1 and Week-14) studies, administered by the subcutaneous (SC) route to cynomolgus monkeys. The off-dose phase of the 26-week study is ongoing so data generated during pretreatment through the end of the dosing period has been evaluated. An *in vitro* cross-reactivity study to evaluate the binding of GSK3511294 to human and cyno tissues has also been conducted.

GSK3511294 binding assessed by immunohistochemistry did not demonstrate specific positive staining in any of the tissues examined with staining restricted to the Positive Control Material (IL-5 coated coupled beads), suggesting little likelihood for non-pharmacological effects.

In the 26 week study, Anti-drug antibody (ADAs) were detected, at Week 26 and/or Week 13, in 3 males given 10 mg/kg/dose and in 1 male and 2 females given 100 mg/kg/dose. GSK3511294 plasma concentrations and serum total IL-5 concentrations were decreased in one male given 10 mg/kg/dose that also had the highest titer for ADA. ADAs were not detected in the 4 week study and quantifiable levels of GSK3511294 in plasma were demonstrated up to the end of collection intervals.

In most animals, a trend towards reduced blood eosinophil counts was observed in both sexes given 100 and/or 10 mg/kg/dose; however, low pretreatment eosinophil values limited the detectable magnitude of the changes. In addition, increases in serum total IL-5 concentrations (up to 70x control) were observed in males and females given 100 and/or 10 mg/kg/dose. The serum total IL-5 concentrations were highly variable and did not exhibit dose-proportionality with increasing dose from 10 to 100 mg/kg/dose. These changes reflect the expected pharmacological activity and extended half-life of GSK3511294.

In the single dose 1 month study (n= 3/sex/grp), adverse vascular inflammation within the kidney, heart, pancreas, spleen, and liver was present in a female given 10 mg/kg: similarly, minimal focal inflammation of a bronchial artery was present in a female given 100 mg/kg. In the absence of detectable ADAs, while a direct effect of the test-item is considered an unlikely cause of the adverse arterial changes in multiple organs, a potential exacerbation of spontaneous immune complex disease by GSK3511294 administration cannot be excluded. Vascular inflammation was not observed in the 26 week repeat dosing study given 2 doses 3 months apart of 10 and 100 mg/kg/dose. Furthermore, the pharmacological mechanism of GSK3511294 to attenuate the eosinophilic inflammatory pathway is precedented and appropriate clinical monitoring will be conducted in this study. Therefore, based on the weight of evidence and in the absence of microscopic findings in the 26 week study, these changes are considered to be of limited clinical relevance.

Increases in QT (up to 55 msec) and QTc (up to 23 msec) observed in the 26 week study at 100 mg/kg are not consistent with the high specificity target interactions of

GSK3511294 to reduce circulating eosinophils by targeting the IL-5 pathway nor with its limited distribution or access to cellular targets, due to its physical size (~149 kilodalton [kDa]) [Vargas, 2013]. Furthermore, no binding to heart tissue was observed in the tissue cross reactivity studies using human and cyno tissue and no histopathological or functional (electrocardiogram [ECG] or heart rate) correlate was observed to explain these findings.

In the 26 week study, as there were no adverse test item-related findings, the no observed adverse effect level (NOAEL) was considered to be 100 mg/kg, the highest dose tested. At this dose, mean Area under concentration-time curve $(AUC)_{0\text{-}2016}$ was 1120000 µg.h/mL, range 898000 to 1290000 µg.h/mL; and mean Maximum observed concentration (C_{max}) was 1390 µg/mL, range 1090 to 1610 µg/mL (gender averaged, Week 14).

While the effect on safety and tolerability of increasing the affinity to IL-5 of GSK3511294 compared with other anti-IL-5 monoclonal antibodies is not known; precedented clinical experience of IL-5 targeting monoclonal antibodies indicate that the GSK3511294 mechanism of action is not anticipated to cause any particular safety concerns and will provide an alternative IL-5 targeting medicine with a longer duration of action. Potential safety considerations with GSK3511294 include the effect on the degree and magnitude of eosinophil suppression, and immune-related non-clinical toxicology findings of unclear cause, and their unclear relevance to humans. Those data, along with pre-clinical data on GSK3511294, support progression of GSK3511294 into this First Time in Humans (FTIH) study of mild-moderate asthmatic patients.

For more information, please refer to the Investigator's Brochure (IB; Section 5).

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of ascending single subcutaneous doses of GSK3511294 in participants with mild to moderate asthma	• Adverse events, serious adverse events, including systemic reactions and local injection site reactions • Vital signs, ECGs, laboratory safety data – including liver and renal chemistry, high sensitivity C-reactive protein (hsCRP), and complement (C3 and C4)
Secondary	
• To evaluate the plasma pharmacokinetics of ascending single subcutaneous doses of GSK3511294 in participants with mild to moderate asthma	• Plasma pharmacokinetic parameters of GSK3511294 after single SC doses: AUC(0-∞), AUC(0-t), AUC(0-Week4), AUC(0-Week12), AUC(0-Week26), %AUCex, Cmax, tmax, tlast, CL/F, Vd/F, λz and t½ when assessable*
• To evaluate the dose response of blood eosinophil counts after ascending single subcutaneous doses of GSK3511294 in participants with mild to moderate asthma	• Ratio to baseline in absolute blood eosinophil count
• To assess the immunogenicity of GSK3511294	• Frequency and titers of binding ADAs to GSK3511294, before and after GSK3511294 administration
Exploratory	
• To assess the effect of single SC doses of GSK3511294 on lung function	• Change from baseline: forced expiratory volume in 1 second ($FEV_{1)}$, forced vital capacity (FVC), peak expiratory flow (PEF)
• Serum total IL-5 following single SC doses of GSK3511294	• Serum total IL-5 levels
• To explore drug specific circulating immune complexes (CIC) after single SC doses of GSK3511294	• Levels of CICs
• To determine the effect of single SC doses of GSK3511294 on serum markers of asthma	• Change from baseline in asthma biomarkers
• To explore the PK/PD (blood eosinophil count) relationship after single SC doses of GSK3511294, if deemed appropriate	• GSK3511294 plasma concentration and blood eosinophil count for determination of Half maximal effective concentration (EC50) and maximum effect, if deemed appropriate

* 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 Week N; %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; Vd/F = apparent volume of distribution after subcutaneous administration; λz = terminal elimination rate constant; t½ = terminal phase half-life.

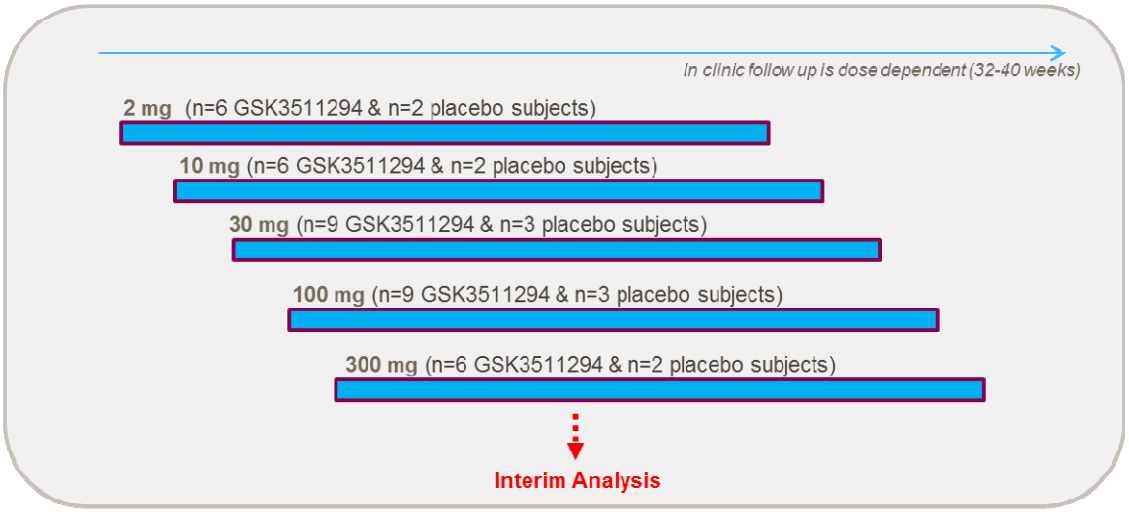
4. STUDY DESIGN

4.1. Overall Design

This is a single ascending dose FTIH study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of subcutaneously administered GSK3511294 in participants with mild to moderate asthma and blood eosinophils ≥ 200 cells/μL.

This study is a multi-center, randomised, double-blind (sponsor clinical pharmacology modelling and simulation [CPMS] and statistician representatives open), placebo-controlled, parallel-group study. Each participant will receive a single dose of GSK3511294 or placebo, as shown in Figure 2.

Figure 2 Summary of GSK3511294 first-time-in-human study design



Notes: Planned single ascending SC doses of GSK3511294 are 2, 10, 30, 100 and 300 mg. Actual dose levels beyond the 2 mg starting dose will be confirmed based on the emerging data. Planned cohort sizes are shown; additional participants may be added to cohorts, if necessary to characterise the pharmacokinetics or pharmacodynamics of GSK3511294. In each cohort, participants will be randomised 3:1 to receive GSK3511294 or placebo. Additional cohorts of up to 12 participants may be added to test additional dose levels or to repeat a dose level already tested, if deemed necessary; however, the dose will not exceed 300 mg. The planned sample size is n=48 participants; the maximum sample size is n=72 participants (excluding replacements for prematurely withdrawn participants).

- Sentinel participants: In each cohort, one placebo and one GSK3511294 participant will be dosed before the remaining participants. Providing no safety issues are identified in the sentinel participants over an observation period of at least 72 hours,

the remaining participants in the cohort may be dosed. The Investigator will discuss any safety concerns with the GlaxoSmithKline (GSK) medical monitor before dosing the remaining participants in a cohort. Sentinel dosing is not required in cohorts investigating a dose lower than or equal to the highest dose tested to date.

4.2. Treatment Arms and Duration

- Cohorts: Planned cohort sizes are as follows:
  - *Cohorts 1 (2 mg), 2 (10 mg) and 5 (300 mg):* 8 participants per cohort – 6 receiving GSK3511294 and 2 receiving placebo
  - *Cohorts 3 (30 mg) and 4 (100 mg):* 12 participants per cohort – 9 receiving GSK3511294 and 3 receiving placebo
- The dose levels, number of cohorts and number of participants per cohort may be adjusted during the course of the study to achieve study objectives based on emerging data from the ongoing analysis. The ratio of active to placebo participants in each cohort will be 3:1.
- Blood eosinophils pre-screen and screening: It is anticipated that a high proportion of the defined asthma population may have blood eosinophil levels that do not meet the inclusion criteria of ≥ 200 eosinophil cells/μL, therefore a blood eosinophils pre-screen assessment will be performed. Participants are eligible to skip the blood eosinophils pre-screening visit and go directly to the screening visit, if they have a documented blood test result within 12 weeks before dosing demonstrating a blood eosinophil level ≥ 200 cells/μL. If blood eosinophil levels within the prior 12 weeks are not available, participants will provide written informed consent at a pre-screening visit followed by a pre-screen assessment of blood eosinophil level. Participants who fulfil the pre-screening criteria will then attend the clinic for a full screening visit. Blood eosinophil level will be measured at screening to confirm eligibility.
- In-patient period: Participants will be admitted the day before dosing, and the minimum post dose in-patient period for all participants will be 72 hours in the UK and 8 days in Germany (Appendix 8). Participants will be monitored for local injection site reactions and allergic reactions for at least 72 hours post dose. In the case of such reactions, appropriate medical treatment will be administered. Participants will be discharged only if the Investigator deems it safe for the participant to leave the unit (For further information regarding the in-patient period in Germany, please refer to Section 12.8.2).
- Follow up period: Participants will receive post-dose assessments during the in-patient period and attend the clinic for further post-dosing assessments, as outlined in the Time and Events Table (Section 7.1). The follow-up period will be up to 40 weeks after dosing, and will be dose dependent, based on the predicted blood eosinophil profile. Participants in cohorts receiving 2 and 10 mg GSK3511294 will attend the clinic visits up to week 32, participants in cohorts receiving 30 mg and 100 mg will attend clinic visits up to week 36, and participants in cohorts receiving 300 mg will attend clinic visits up to week 40. (For unplanned dose levels, the duration of follow-up will be documented in Note to File.) The follow-up period for

any participant may be adjusted, if necessary, based on the anticipated duration of action or any safety concerns that may emerge during the study.

- Total duration: The scheduled maximum study duration for each participant who receives GSK3511294 or placebo will be up to 44 weeks (excluding pre-screening for blood eosinophils), including up to 28 days for screening, 4 days as an in-patient in the UK and 9 days in Germany (Appendix 8), and up to 40 weeks post-dosing to investigate the PD (blood eosinophil count) and safety profile.

4.3. Dose Escalation

- The Dose Escalation Committee (DEC) will consist of the Principal Investigator(s) (or appropriate designee), GSK Medical Monitors, GSK Study Team Leader, GSK Clinical Pharmacology Modelling and Simulation (CPMS) representative, a GSK Global Clinical Safety and Pharmacovigilance (GCSP) representative and GSK Statistician representative. The GSK CPMS and statistician representatives will remain unblinded throughout the course of the study.
- The DEC will select and approve doses throughout the study, and will review available data from all participants in each cohort before initiating each new dose level. Dose escalation may occur only after review of the following data at the highest dose level tested to date: at least 4 weeks' post-dose safety data and at least 2 weeks' post-dose PK data from at least 4 participants on active treatment; and at least 72 hours' post-dose safety data from the remaining participants in the cohort. In the unlikely event that one or more of the remaining participants discontinued the study within 72 hours after dosing, all available safety data from that/those participants will be reviewed.
- Owing to the mechanism of action of GSK3511294, blood eosinophil results have the potential to unblind. Therefore, study personnel will be blinded to post-dose blood eosinophil results for individual participants. The sponsor CPMS and statistician representatives will review individual data, but summary statistics for the active group only will be provided to the remaining members of the DEC for the purposes of dose selection. Similarly, to minimise the risk of unblinding during DEC meetings, no individual PK data will be discussed; summary statistics only will be provided to blinded members of the DEC. If ongoing analyses are based on an incomplete cohort, to avoid unblinding, the DEC (except the GSK CPMS and statistician representatives) will be blinded to the number of participants included in the summaries of PK and blood eosinophils for that cohort.
- This protocol allows some alteration from the currently outlined dosing schedule, but the maximum single dose will not exceed 300 mg.
- The dose will be increased only if safety and tolerability at previous dose levels are acceptable, and also if the predicted exposure (upper 95% prediction interval for C_{max} and AUC) at the next dose level does not exceed the mean exposure observed at the NOAEL in monkey in the 26 week toxicity study (100 mg/kg).

mean C_{max}: 1390 µg/mL	mean AUC_{0-2016} 1120000 µg.h/mL

- The dose will not be escalated, nor will a dose level be repeated, if, at that dose level:

- one or more of the study halting criteria are met (see Section 5.5)
- one or more participants has experienced at least one of the criteria for potential type III hypersensitivity/immune complex disease, and there is ongoing clinical concern about the participant's condition (see Section 5.4.2)
- one or more participants has a QTcF > 500 msec or uncorrected QT > 600 msec, or an increase in QTcF > 60 msec, in the absence of any other identifiable reason (e.g. concomitant medication). In such a scenario, if after review of all clinical safety data for the participant(s), the increased QT is considered to be isolated and not clinically significant in the opinion of the medical monitor and investigators, dose escalation and/or dosing of further patients at the dose level at which the event was observed can occur only after ethics and regulatory approval of a substantial amendment.

4.4. Type and Number of Participants

The total number of participants pre-screened/screened will meet the need to randomise a sufficient number of participants in order to meet the study objectives. It is anticipated that after completion of successful screening, approximately 48 mild to moderate asthmatic participants, with blood eosinophils ≥ 200 cells/μL at screening, will be randomised. As the number of cohorts and number of participants per cohort are flexible, the protocol allows randomization of up to 72 participants (excluding replacements for prematurely withdrawn participants), split between about 6 clinical sites.

If participants prematurely discontinue the study, replacement participants may be recruited at the discretion of the Sponsor in consultation with the investigator in order to achieve the objectives of the study.

4.5. Design Justification and Choice of Population

The current study is a double-blind (sponsor CPMS and statistician representatives open), placebo controlled, parallel group, single ascending dose, FTIH study of GSK3511294, with safety and tolerability as the primary objective. A key secondary objective is to confirm if the extended pharmacology of GSK3511294 observed preclinically translates into humans. Hence, the magnitude and duration of reduction in blood eosinophils in a disease setting of eosinophilic asthma will be assessed. In order to fully assess the GSK3511294 PK/PD profile, data will be collected for various follow up periods post dose (dependent on dose level) up to approximately 40 weeks.

FTIH population selected: Mild to moderate asthmatics with an eosinophilic phenotype have been selected based on the following considerations.

- Although GSK3511294 is a new molecular entity, and this study represents its first investigation in humans, its mechanism of action of IL-5 antagonism is precedented. Anti IL-5 mAbs, mepolizumab and reslizumab, have been investigated in the clinic in severe eosinophilic asthma, and were shown to have an overall favourable safety profile. As of 23 September 2016, approximately 2000 people have been exposed to

at least one dose of mepolizumab in completed GSK-sponsored clinical studies across various eosinophilic-mediated indications.

- Mepolizumab dose response for blood eosinophil reduction is consistent between participants with mild to moderate asthma and those with severe asthma. Also, blood eosinophils and IL-5 are elevated in mild-moderate asthmatics relative to healthy participants. Therefore, a study in mild-moderate asthmatics with blood eosinophils ≥ 200 cells/μL at screening, provides an opportunity to investigate the effect of GSK3511294 on the blood eosinophil profile, to better inform dose selection and the dosing interval in later phase studies. However, based on the data with mepolizumab, treatment benefit is not expected in a mild-moderate asthma patient population.

Overall, a FTIH study of participants with mild to moderate controlled asthma (defined in Section 5), on *prn* SABA, and regular ICS or an ICS/LABA combination, is considered justified to achieve the objectives of this FTIH study with GSK3511294.

4.6. Dose Justification

Pharmacokinetics: Mepolizumab and GSK3511294 plasma concentration data, generated from a single dose cynomolgus monkey PK/PD study, were modelled simultaneously along with the toxicokinetics (TK) data from the one month toxicity study, and showed that only systemic clearance differed between the two molecules. The volume of distribution of the central and peripheral compartment, as well as the inter-compartmental clearance, were similar. Clearance decreased by an estimated 1.9-fold with GSK3511294 compared to mepolizumab, and this fold reduction is expected to be preserved between monkey and human. Predicted human exposure following single GSK3511294 SC administration at the proposed doses in the study were estimated using the known mepolizumab PK in human adjusted by the predicted fold difference in clearance determined from the pre-clinical studies (Table 1 and Figure 3). Absolute bioavailability was assumed to be 75%, similar to mepolizumab. The predicted human systemic clearance (CL) is 0.00465 L/h or 0.112 L/day and the plasma elimination half-life is approximately 37 days.

IL-5 binding affinity: Due to the limitation of various *in vitro* assays, GSK3511294 binding affinity is difficult to measure, but is anticipated to be 20-30 fold more potent than mepolizumab. Simulations to reproduce the total IL-5 and blood eosinophil profiles observed in the cynomolgus monkey PK/PD study were generated using a PK/PD model developed previously based on mepolizumab pharmacology data. Whilst acknowledging the uncertainty due to the small sample size in the cynomolgus monkey study, simulations seem to support a minimum of a 30-fold higher binding affinity of GSK3511294 compared with mepolizumab.

Estimation of GSK3511294 therapeutic dose and frequency of administration: The approved mepolizumab therapeutic dose in severe eosinophilic asthma is 100 mg SC administered every 4 weeks. It is hypothesised that if the blood eosinophil reduction observed at GSK3511294 trough concentrations in steady-state conditions is similar to that observed at mepolizumab 100 mg SC trough concentrations, it is likely that similar 'clinical efficacy' (reduction in asthma exacerbations) to mepolizumab will also be

observed in relevant clinical populations. Therefore, simulations using a semi-mechanistic stochastic model were generated, incorporating the clearance (1.9-fold) and binding affinity (30-fold) improvements observed in monkeys, assuming the findings in monkey will translate into humans. The GSK3511294 simulations showed that a SC dose of GSK3511294 between 30−100 mg administered every 6 months could be a plausible therapeutic dose and dosing interval.

GSK3511294 starting dose: Given the clinical experience with IL-5 antagonism as a mechanism of action, a 2 mg SC dose of GSK3511294 is justified as a starting dose. The 2 mg SC dose is anticipated to correspond to an average maximum reduction in blood eosinophils of approximately 75% (occurring approximately 2 weeks post-dosing), with a return to approximately 50% of the maximum response at around 150 days post dose (Figure 4). This level of blood eosinophil reduction is less than that previously observed in the clinic with repeat dosing of mepolizumab that was well tolerated. Therefore, this sub-therapeutic GSK3511294 2 mg starting dose is anticipated to: be well tolerated; offer the possibility to evaluate the blood eosinophil return towards baseline over an operationally reasonable period of time; and hence the opportunity to assess the *in vivo* potency of GSK3511294 in human. The proposed starting dose of 2 mg is 3500-fold lower than the NOAEL dose established in the 26-week toxicity monkey study (dose expressed in mg/kg and assuming a 70 kg participant) and the predicted AUC 3470-fold lower than the exposure observed at the NOAEL dose (Table 1).

SAD increments: The proposed SC single doses to be investigated in this FTIH study are 2, 10, 30, 100 and 300 mg. These doses correspond to dose increments of 5-fold, 3-fold, 3.3-fold and 3-fold, respectively, and are considered acceptable considering the precedence of the IL-5 antagonism mechanism of action. Furthermore, sentinel participants are planned for each escalating dose level.

Maximum GSK3511294 dose: In this single ascending dose FTIH study, the maximum proposed GSK3511294 SC dose is 300 mg which is 23-fold lower than the NOAEL dose established in the 26-week toxicity monkey study (dose expressed in mg/kg and assuming a 70 kg participant). This dose will provide safety data at a dose 3-fold above the upper limit of the predicted therapeutic GSK3511294 SC dose range of 30–100 mg for severe asthma (predicted based on the GSK3511294 monkey PK/PD data). A dose of 300 mg remains operationally feasible and is expected to be tolerated by participants with regard to number of injections (3x100 mg SC injections). Furthermore, the proposed 300 mg maximum GSK3511294 SC dose, with an estimated average maximum reduction in blood eosinophils of approximately 93% (Figure 4), is anticipated to be tolerable given that 750 mg Intravenous (IV) mepolizumab administered every 4 weeks for at least 12 months (average 88% blood eosinophil reduction at lowest concentration of a drug just before the next dose [Ctrough]) was found to be well tolerated. Redundancy mechanisms exist to promote eosinophil production and therefore a complete (100%) suppression of blood eosinophils is not expected even at the maximum proposed 300 mg SC dose of GSK3511294. The predicted AUC at this dose is 23-fold lower than the exposure observed at the NOAEL dose of 100 mg /kg in the 26 week toxicity monkey study (Table 1).

Figure 3 **Predicted mean with 95% CI GSK3511294 plasma concentration-time profiles at the planned single SC doses of 2, 10, 30, 100 and 300 mg (with mepolizumab as a reference)**

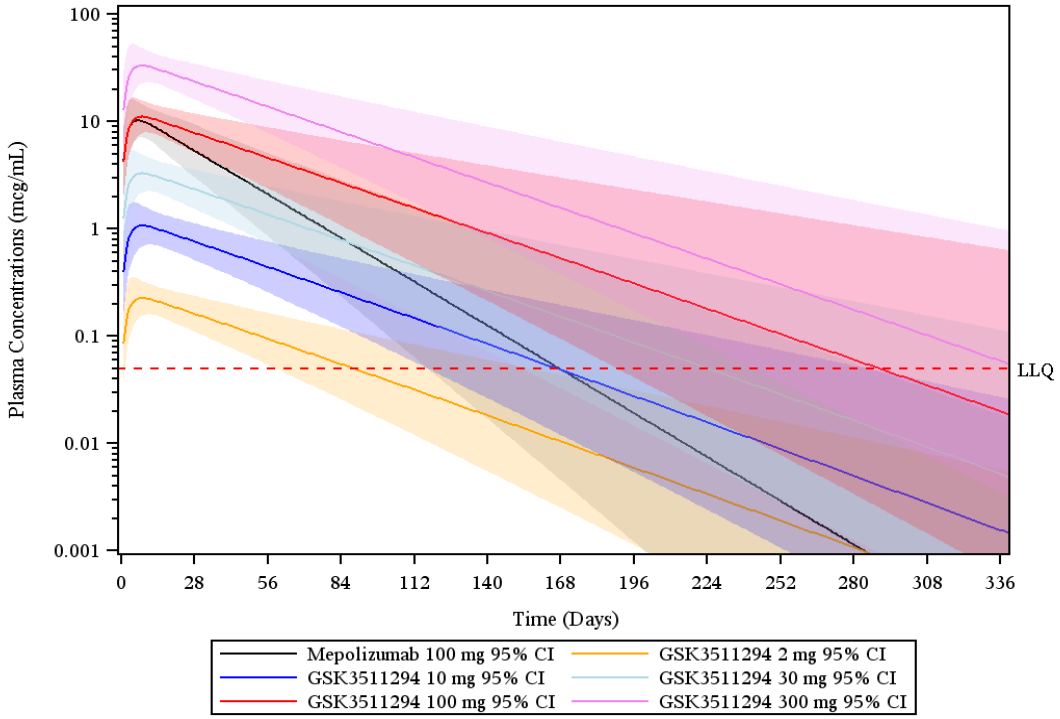


Figure 4 **Predicted mean with 95% CI GSK3511294 blood eosinophil ratio-time profiles at the planned single SC doses of 2, 10, 30, 100 and 300 mg (with mepolizumab as a reference)**

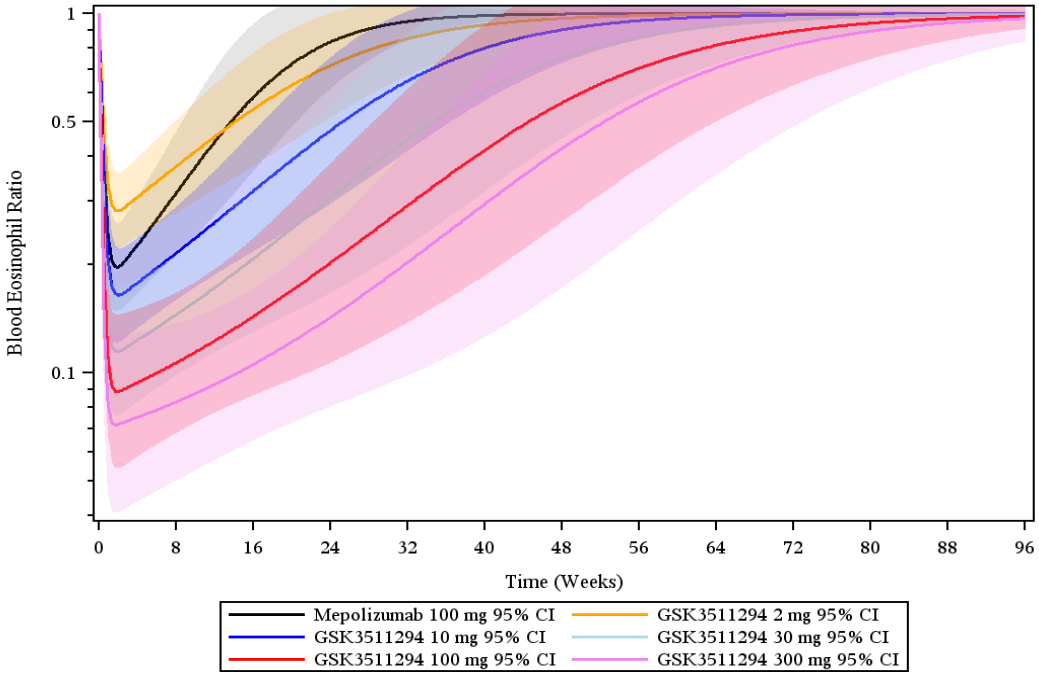


Table 1 Safety margins when comparing monkey NOAEL data (cross-reactive species) with predicted human data at the proposed doses of GSK3511294 administered SC ('safety cover')

Predicted Human Cmax and AUC				Safety cover (vs. Monkey NOAEL)		
Dose (mg)	**Dose (mg/kg)[1]**	**Cmax (µg/mL)**	**AUC (µg*h/mL)**	**Dose cover[2]**	**Cmax Cover**	**Cover AUC**
2	0.03	0.226	323	3500x	6156x	3471x
10	0.14	1.13	1613	700x	1231x	694x
30	0.43	3.39	4840	233x	410x	231x
100	1.43	11.3	16132	70x	123x	69x
300	4.29	33.9	48396	23x	41x	23x

1. assuming a 70 kg participant
2. dose (expressed in mg/kg) cover

4.7. Benefit:Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK3511294 can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.7.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3511294]		
▪ Systemic reactions including allergic reactions.	▪ Systemic reactions including allergic reactions, with the most severe form being anaphylaxis (see Appendix 9), are potential risks associated with mAbs. ▪ Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm or hypotension) have occurred following mepolizumab administration in asthma patients.	▪ Sentinel participants will be used at all escalating dose levels and monitored for at least 72 hours post dose before dosing the remainder of the cohort. ▪ All participants in the UK will have a minimum 72 hour post dose in-patient monitoring period at experienced phase 1 study sites to ensure any late reactions are captured. In Germany this post dose in-patient monitoring period will be 8 days (Appendix 8). ▪ Participants with a history of an allergic sensitivity to biologic agents are excluded. ▪ Any observed reactions will also be treated based on investigator medical judgement (with medical monitor consult as needed). ▪ Investigators will be asked to assess events they consider to represent systemic reactions and events of anaphylaxis against Sampson diagnostic criteria for anaphylaxis (Appendix 9)
▪ Type III Hypersensitivity (Immune complex deposition in kidney, heart, pancreas, spleen, liver and lung)	▪ 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	▪ Participants with history of renal disease, evidence of protein or blood on urinalysis or abnormal kidney function will be excluded, as will be patients with history or signs of immunologically active disease (defined by

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 whether immunogenicity in humans after dosing will result in the formation of pathogenic immune complexes as data from preclinical models is not necessarily predictive of immune complex disease in human effects.	low C3 or low C4), previous history of vasculitis and patients with a significantly elevated Alanine aminotransferase (ALT) or history of liver disease. ▪ Safety evaluation of individual participants will be in place, with data being reviewed on an ongoing basis by the Sponsor and Investigators. Any clinical signs that might indicate immune complex disease will be reported to the sponsor's medical monitor within 24 hours of the investigator becoming aware of the event, regardless whether the event is considered serious or non-serious. Participants will be investigated and treated as clinically indicated (Appendix 3). ▪ Targeted monitoring of laboratory data (tests shown in Section 7.3.6 and time points shown in Section 7.1) will include urinalysis to detect haematuria and microalbuminuria and clinical chemistry parameters. ADA and immune complex concentrations, trends in C3 and C4, platelets and inflammatory markers, over time will also be assessed. ▪ Halting and monitoring rules, based on the clinical findings, are defined to minimise the risk to participants (Section 5.4 and Section 5.5).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
▪ Immunogenicity, ADAs	▪ Biopharmaceutical products may elicit ADAs, which have the potential to modulate PK or PD, or to produce adverse reactions. This is the GSK3511294 FTIH study, hence the ADA response in humans is unknown.	▪ A single dose of GSK3511294 will be administered to a participant. ▪ Binding ADAs to GSK3511294 will be measured, and adverse event profile will be compared between ADA-positive and ADA-negative participants.
▪ 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 placebo-controlled severe asthma studies, an increase in the incidence of local injection site reactions has been observed with SC mepolizumab administration compared with placebo (8% vs. 3%). There have been no reports of severe reactions. Pain, erythema, swelling, itching, and burning sensation were the most common symptoms reported.	▪ Routine monitoring of participants for at least 72 hours after dosing in the UK and 8 days in Germany (Appendix 8).
▪ QTc prolongation	▪ Four monkeys in the 6-month repeat dose monkey study administered 100 mg/kg/week were observed to have QTc prolongation (mean change of 18 msec relative to vehicle control value) during Week 14. ▪ relative to control) at week 14 in the 100 mg/kg dose group only.	▪ ECGs will be performed on a regular basis and should there be any QTc abnormality patients will be monitored more frequently and management instituted as deemed relevant by the Investigator in liaison with the medical monitor. ▪ Participants with QTc prolongation on screening will be excluded. Participants with a history of cardiac disease, Left Bundle Branch Block, Right Bundle Branch Block, severe hypertension,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		QTc abnormality or arrhythmia will be excluded as will participants with a relevant family history.
▪ Alterations in immune response, potentially leading to increase in infections	▪ This is a theoretical concern with drugs that affect the immune system. The known biology of IL-5 and eosinophils suggest that inhibiting IL-5 is unlikely to induce an immunosuppressive effect. ▪ Eosinophils may be involved in the immunological response to some helminth infections.	▪ Individuals with a recent history of an opportunistic infection, a current respiratory or other latent/chronic infection, or positive history or test for hepatitis B/C or human immunodeficiency virus (HIV) are excluded. ▪ Receipt of a live vaccine within 4 weeks of screening is exclusionary, and live vaccines are contraindicated during the study period. ▪ Major surgery within 90 days of screening and/or planned surgery during the study are exclusionary. ▪ Current study will be conducted in countries where gastro-intestinal parasitic infections are rare. Patients with parasitic (helminth) infections within 6 months of screening are excluded, along with those who have travelled to (within the 6 months before dosing) or intend to travel to (within 1 year after dosing) countries with a high prevalence of parasitic disease.
▪ 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	▪ Females of reproduction potential will be excluded from the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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, 2015], the risk of adverse effects on spermatogenesis is considered minimal.	▪ It is expected that spermatogenesis will not be affected by GSK3511294, so males will not be required to use contraception during the study.
Study Design		
▪ Duration of in-patient stay after dosing	▪ Tmax of GSK3511294 is expected at 7−10 days after dosing. However, any significant side effect of GSK3511294 in the time to Tmax is most likely to be an anaphylactic reaction, which would occur in the first 72 hours after dosing. The predicted PK profile indicates approximately 80% of Cmax at 72 hours after dosing. Participants will have a minimum 72 hour in patient monitoring period at experienced phase 1 study.	▪ In the UK, Investigators will review available safety data up to 72 hours to confirm participants are well enough to leave the clinical unit. In Germany, in response to regulatory comments, participants will be in-patient until at least 8 days after dosing. ▪ Participants will receive a medical alert card, with details of the study, clinical site and Investigator, when they are discharged from the unit. They will be instructed to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Therefore, to minimise the inconvenience to participants, they may be discharged from the clinical unit 72 hours (or longer) after dosing, provided that the Investigator considers them well enough to leave.	contact the unit with any safety concerns they might have, and to show the medical alert card to any other medical professional they might consult.
▪ Duration of the study	▪ Final follow-up at all dose levels is scheduled to exceed 5 terminal t½ of GSK3511294 (predicted t½ is about 37 days; shortest time to follow-up after dosing is 225 days). Owing to the increased affinity of GSK3511294 for IL-5, blood eosinophils levels may still be reduced at the final scheduled follow-up visit, particularly at higher dose levels. However, reduction in blood eosinophils is not considered to be a safety concern – residual levels of blood eosinophils are expected to be present, and there have been no safety signal from chronic dosing with mepolizumab, reslizumab or benralizumab.	▪ Follow-up will be extended in any participant for whom there are safety concerns, until that concern is discharged.

4.7.2. Benefit Assessment

- No clinical benefit is expected for the mild to moderate asthmatics who are to be enrolled into this FTIH study, as evidence for clinical benefits using mepolizumab and reslizumab have been demonstrated in the severe asthmatic population.
- This single ascending dose, FTIH study in mild to moderate asthmatics (with blood eosinophils ≥ 200 cells/μL) will not only provide initial safety, tolerability, immunogenicity, and pharmacokinetic data, but also an understanding of the relationship between GSK3511294 dose and blood eosinophil reduction, to better inform dose selection and dosing interval in the subsequent studies of the clinical development program.

4.7.3. Overall Benefit:Risk Conclusion

Although no clinical benefit is expected for recruited participants, overall the benefit:risk balance for this FTIH study to be performed in mild to moderate asthmatics is considered acceptable. The study provides the opportunity to generate key PK and PD data, as well as safety and tolerability information, in an eosinophilic population, thereby supporting subsequent progression into the targeted severe eosinophilic asthma population. Close monitoring of participants for standard safety concerns in FTIH studies of biologics will be performed.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact participant eligibility is provided in the IB (Section 3).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A participant will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. **Between 18 and 65 years** of age inclusive, at the time of signing the informed consent.

TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. **Blood eosinophils** of ≥ 200 cells/µL at screening. 3. **Asthma**: A physician diagnosis of asthma (mild or moderate, as defined by the Global Initiative for Asthma (GINA), 2017) at least 12 months prior to the start of the study. The reason for diagnosis of asthma should be documented in the participant's source data, including relevant history. If available, investigations – specifically evidence of airway hyperresponsiveness, airflow variation (peak flow rate or FEV_1) or reversible airflow obstruction, should also be documented in the participant's source data. *NOTE:* • *Airway hyper-responsiveness is defined by a methacholine or histamine concentration of <8 mg/mL producing a ≥ 20% fall in FEV_1.* • *Airflow variation is defined as a variation in peak flow rate (the difference between the highest and lowest peak expiratory flow rate expressed as a percentage of the average peak expiratory flow rate) of > 20% over a series of measurements or a variation in FEV_1 > 15% when measured on separate occasions.* • *Reversible airway obstruction is defined as increase in FEV_1 of ≥ 12% over baseline AND an absolute change of ≥ 200 mL, following 4 inhalations of albuterol/salbutamol inhalation aerosol/spacer (or equivalent nebulised treatment with albuterol/salbutamol solution).* 4. **Asthma status:** A screening pre-bronchodilator FEV_1 ≥ 60% of predicted normal value. • *NOTE: Predicted values based upon European Respiratory Society guidelines [*Quanjer*, 2012].* 5. **Asthma control:** Asthma Control Test score > 19. 6. **hsCRP** of < 10 mg/L at screening. 7. **Otherwise healthy** (other than the acceptable conditions of asthma and other atopic diseases, including allergic rhinitis and atopic dermatitis) based on a screening medical history, physical examination, vital signs, ECG assessment, pulmonary function testing, and clinical laboratory results. *NOTE: A participant with abnormal clinical 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 Medical Monitor) agree and document that the finding is*

unlikely to introduce additional risk factors and will not interfere with the study procedures. In the event of out-of-range results of safety tests, the tests may be repeated once within the screening window. If a retest result is again outside the reference range and considered clinically significant by the investigator and GSK medical monitor, the participant will be considered a screen failure.

8. **Asthma therapy:**
   - Maintained controlled on as needed SABA and one of the following:
   - stable dose of ICS
   - stable dose of combination therapy: ICS/LABA

   NOTE: the ICS dose should be up to a maximum daily dose shown in Table 2, and stable for at least 12 weeks prior to the study treatment.

Table 2 Maximum Allowed Daily Doses of Inhaled Corticosteroid (ICS)

Inhaled Corticosteroid	Max Daily Dose (μg)
Beclomethasone dipropionate (CFC)	1000
Beclomethasone dipropionate (HFA)	400
Budesonide (DPI)	800
Ciclesonide (HFA)	320
Fluticasone priopionate (DPI)	500
Fluticasone furoate (DPI)	100
Mometasone furoate	440
Triamcinolone acetonide	2000

CFC –Chorofluorocarbonate, DPI – Dry Powder inhaler, HFA-: hydrofluoroalkane propellant

WEIGHT

9. **Body weight** ≥ 50 kg, and **body mass index (BMI)** of 19-32 kg/m^2 inclusive.

SEX

10. **Male and female participants.**

    a. Females: a female participant is eligible to participate if she is not pregnant (see Appendix 6), not breastfeeding, and not a woman of childbearing potential as defined in Appendix 6.

    b. Males: 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.

INFORMED CONSENT
11. Capable of giving signed **informed consent** as described in Section 10.2, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A participant will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. **Asthma exacerbation:** Any asthma exacerbation requiring systemic corticosteroids within 12 weeks of screening, or that resulted in overnight hospitalization requiring additional treatment for asthma within 6 months prior to screening. 2. **A history of life-threatening asthma**. Defined as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the last 5 years. 3. **Significant pulmonary diseases, other than asthma, including (but not limited to):** pneumonia previously requiring hospital admission, pulmonary fibrosis, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or other significant respiratory abnormalities. 4. **Respiratory Infection:** Suspected or confirmed bacterial or viral infection (including tuberculosis) of the upper or lower respiratory tract, sinus or middle ear that occurred within and/or has not resolved within 4 weeks of screening that: • led to a change in asthma management OR • in the opinion of the Investigator, is expected to affect the participant's asthma status or the participant's ability to participate in the study. *NOTE: Participants can be rescreened once to allow for an adequate time period between resolution of the infection and randomisation.* 5. Positive for **hepatitis B** surface antigen (HBsAg) at screening. (Please refer to Appendix 8 for country specific requirements for Germany) 6. Positive **hepatitis C** antibody test result at screening, or within 3 months prior to first dose of study treatment. *NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C Ribonucleic acid (RNA) Polymerase chain reaction (PCR) test is obtained. Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.* 7. Known **immunodeficiency** (other than that explained by the use of corticosteroids), including a positive test for **HIV** antibody at screening.

8. **Latent or chronic infections** (e.g., genital herpes, urinary tract infections) or at risk of infection (e.g., significant trauma or infection within the 90 days before screening).
9. **Opportunistic infection** within 6 months prior to screening (e.g., a non-tuberculous mycobacterial infection or cytomegalovirus, pneumocystosis, aspergillosis).
10. **Parasitic infestation** within 6 months prior to screening, or have travelled to a country with a high prevalence of such infections in the 6 months before screening, or intend to do so in the year after dosing.
11. **Live vaccine** within 4 weeks prior to screening, or intention to receive live vaccine during the study.
    NOTE: Attenuated or non-live vaccines are acceptable, if > 5 days before dosing.
12. **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 or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).*
13. A personal history of **severe hypertension, arrhythmia, Right Bundle Branch Block, or Left Bundle Branch Block**, or a family history of **sudden unexplained death, long QT, familial cardiac syndrome, or cardiomyopathy**.
14. **Alanine aminotransferase (ALT) >1.5xUpper limit of normal (ULN).**
15. **Bilirubin >1.5xULN.** Isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%.
16. **Current or chronic history of liver disease**, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
17. **Any history or presence of clinically relevant** cardiac or cardiovascular, gastrointestinal, hepatic, renal, metabolic, haematological, neurological, osteomuscular, articular, psychiatric, systemic, ocular, or infectious disease or immunodeficiency, or signs of acute illness, or any other illness or condition that, in the opinion of the investigator (in consultation with the medical monitor), would adversely affect the participant's participation in this study.
    Note: Atopic diseases, like allergic rhinitis or atopic dermatitis, are not exclusionary.
18. **History of cancer:** a previous history of cancer in remission for less than 5 years prior to screening (except for localised carcinoma of the skin that had been resected for cure) or current malignancy.
19. **A positive drug/alcohol test** before dosing, OR any history of drug abuse OR regular alcohol consumption within 6 months of the study defined as:
    - An average weekly intake of > 14 units alcohol. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.

20. **Current smokers or ex-smokers** who have given up smoking for < 12 months and/or have a smoking pack history of > 5 pack years (1 pack year = 20 cigarettes per day for 1 year or 5 cigarettes per day for 4 years).
21. **Urinary cotinine levels** indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening.
22. **Anticipated non-availability and/or risk of non-compliance** with study visits and procedures, or unwillingness or inability to follow the procedures outlined in the protocol.
    NOTE: Vulnerable Subjects (e.g those in detention) and those not able to communicate in the native language of the attending study site would be excluded.
23. **The participant has participated in a clinical trial** and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
24. **Exposure to more than 4 investigational medicinal products** within 12 months prior to the first dosing day.
25. **History of sensitivity to any of the study medications**, or its components, or a history of drug reaction or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
    NOTE: This includes any previous allergic reaction to biologic agents.
26. **Major surgery** within 90 days prior to screening, or planned in-patient surgery or hospitalisation during the study period
27. **Donation or loss of blood** or blood products in excess of 500 mL within the 3 months before dosing.
28. History of **renal disease**, abnormal kidney function or evidence of persisting or clinically relevant protein or blood on urinalysis.
29. History or signs of **immunologically active disease** (including the presence of low C3 or low C4) or thrombocytopenia.
30. History of **vasculitis**.

CONCOMITANT MEDICATIONS

31. **Prohibited Medications:** Participants are excluded if they are undergoing desensitization therapy, or have received any of the following medications as indicated prior to screening:
    - anti- Immunoglobulin E (IgE) therapy (within 6 months)
    - anti-IL5 (within 6 months)
    - oral or injectable corticosteroids (within 8 weeks)
    - long acting muscarinic antagonist (LAMA) or leukotriene receptor antagonist (LTRA) therapy (within 8 weeks)
    - drugs that can prolongate the QT interval (see Table 3)

OTHER
32. **Employment:** participants who are employees of the sponsor or clinical unit are excluded.
33. Vulnerable subjects, e.g., participants kept in detention, protected adults under guardianship, trusteeship and soldiers, or participants committed to an institution by governmental or juridical order.

5.3. Pre-screening/Screening/Baseline/Run-in Failures

Pre-screening failures are defined as participants who consent to participate in a clinical trial, attend the Pre-screening visit but do not meet the criteria for the screening visit (blood eosinophils ≥200 cells/μL). Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently randomised. To ensure transparent reporting of screen failure participants, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.5). Participants who would not have been a screen failure on the basis of the entry criteria in the current version of the protocol may be rescreened for entry into the study. Participants who could not be dosed for logistical reasons within the permissible screening window after passing screening for a cohort, may be rescreened for entry into a subsequent cohort. Rescreened participants should be assigned a new participant number.

5.4. Study Withdrawal Criteria

5.4.1. Individual participant withdrawal from the study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Procedures planned for the participant's last visit should be done at the time of early withdrawal. Furthermore, if a PK sample was not planned at the participant's last visit, it should be taken at early withdrawal.

5.4.1.1. 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 in relation to a participant who fails to attend the clinic for a required study visit:

- The site must attempt to contact the participant and re-schedule the missed visit as soon as possible.
- The site must 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.
- In cases where the 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, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.4.2. Criteria for follow up of potential Type III Hypersensitivity/ Immune Complex Disease

Owing to the adverse effects consistent with immune complex disease, that were observed in the 1-month, but not 6-month, monkey studies, events consistent with type III hypersensitivity/immune complex disease will be reported to the GSK medical monitor within 24 hours of the Investigator becoming aware of the event, regardless whether the event is considered serious or non-serious. Treatment for the event will be given as medically required (see Appendix 3 regarding proposed management). If possible, PK, ADA and CIC samples should be taken at the time of the event.

- A combination of general symptoms associated with hypersensitivity or other potential clinical manifestations of immune complex disease. Symptoms include but are not limited to:
  - persistent* fever
  - persistent* muscle and joint pain
  - persistent* rash
  - symptoms of peripheral neuropathy, like numbness or weakness, and associated with progressive decrease in complement markers (C3, C4)
- * Persistent is considered to be longer than 2 days.
- Urticaria.
- Clinical symptoms suggestive of serum sickness (e.g., fever, general ill feeling, hives, itching, joint pain, rash, swollen lymph nodes).
- Persistent thrombocytopenia, elevated hsCRP, or kidney or liver function tests indicative of organ damage:

- reduced platelet count
- elevated hsCRP
- elevated serum creatinine
- urinary albumin-creatinine ratio > 3 mg/mmol in the absence of a urinary tract infection
- persisting urinalysis abnormality for longer than 1 week
- macroscopic haematuria, without a clear cause (such as trauma)

- Participants who experience any of the above events will be withdrawn from the study (ie they won't take part in further study procedures, if clinically indicated; however, they will be followed up for safety, as required). If the participant is well enough to do so, they may continue in the study.

5.4.3. Criteria for increased monitoring of individual participants

5.4.3.1. 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 2 for guidance regarding increased monitoring of liver chemistry and required actions and follow-up assessments.

5.4.3.2. 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 hour ambulatory Holter monitor and subsequent repeat assessment at 48 hours *.

- 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.

***** To remain under observation if QTcF (or QT if > 600 msec) remains the same/increases on assessment at 24 (end of direct observation) and 72 hours periods (after 48 hour Holter monitor) and for 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.

5.5. Study halting criteria

If one or more of the following criteria are met, the study will be halted 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 at least 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 at least possibly related to study drug
  - an episode of angioedema that is at least possibly related to study drug
  - a biopsy showing features of immune complex disease
  - 2 or more participants have severe Adverse Event (AEs) at least possibly related to study drug

Participants who have been dosed at the time of the study halt will continue in the study, as planned. Further participants may be dosed only if, after review, the sponsor and investigators consider it safe to do so and only after ethics and regulatory approval of a substantial amendment.

5.6. Participant and Study Completion

A completed participant is one who has completed all phases of the study including the follow-up visit. The end of the study/clinical trial is defined as the last visit of the last participant in the trial globally. If the study is terminated early, the end of study/clinical trial is defined as the last visit of the last participant in the trial globally, or the date on which the sponsor decides to end the study, whichever is later.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the participant as per the protocol design.

	Study Treatment	
Product name:	**GSK3511294 Injection, 150 mg/mL**	**0.9% w/v Sodium Chloride Injection (placebo)**
Formulation description:	The GSK3511294 drug product is formulated with L-Histidine, monohydrochloride, monohydrate; L-Histidine; Trehalose dihydrate; L-Arginine hydrochloride; Disodium Edetate Ethylenediaminetetraacetic acid (EDTA); L-Methionine; and polysorbate 80	0.9% w/v Sodium Chloride
Dosage form:	Solution for injection	Solution for injection
Unit dose strength(s)/Dosage level(s):	150 mg/mL (1 mL nominal volume) in a 3 mL glass vial; Dosage levels vary per cohort.	Volume to match active dose
Route of Administration	Subcutaneous Injection. 1 mL solution per injection. <u>For dose levels below 100 mg</u>: The study medication must be diluted in 0.9% w/v sodium chloride to a concentration equivalent to the dose so that the entire dose can be administered using a single 1 mL injection (e.g. 1 mL administration of diluted 2 mg/mL concentration for 2 mg dose). <u>For dose level at 100 mg</u>: The study medication must be diluted in 0.9% w/v sodium chloride to 100 mg/mL. One 1 mL injection of the diluted 100 mg/mL study medication will be administered per participant to achieve 100 mg dose. For dose levels above 100 mg: The study medication must be diluted in 0.9% w/v sodium chloride to a concentration between 50-100 mg/mL such that one to three 1 mL injections of the diluted study medication can be administered per participant to achieve above 100 mg to 300 mg dose (e.g. two 1 mL injections of diluted 65 mg/mL concentration for 130 mg dose). The multiple dose injection can be injected in the upper arm, up to 3 per arm at least 5 cm apart.	To match active (i.e. the same volume and number of injections as the participants on GSK3511294 in that cohort)
Dosing instructions:	Details can be found in the Study Reference Manual	To match active
Physical description:	Clear or opalescent, colourless or yellow to brown liquid. Essentially free from visible particulates.	Refer to product insert

	Study Treatment	
Manufacturer/ Source of procurement:	GSK	Locally sourced by trial site

Rescue medication (salbutamol/albuterol) shall be supplied to participants at Screening for use during the study. This should be stored and administered in accordance with the manufacturer's recommended instructions. Replacement rescue medication will be supplied to participants, as required.

6.2. Treatment Assignment

Participants will be randomised in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Participants in each cohort will be allocated in a 3:1 ratio (active:placebo).

In each cohort, dosing will be staggered: one participant will receive GSK3511294 and one participant will receive placebo at least 72 hours before the remaining participants in that cohort are dosed. Providing no safety issues are identified in the sentinel participants over an observation period of at least 72 hours, the remaining participants in the cohort may be dosed. Sentinel dosing is not required in cohorts investigating a dose lower than or equal to the highest dose tested to date.

A separate randomisation schedule will be created for each cohort. Two strata will be created within each randomisation schedule; to capture the randomisation for the sentinel participants and the randomisation for the remaining participants in each cohort.

6.3. Blinding

This will be a double blind (sponsor CPMS and statistician representatives open). The following will apply.

- The investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.
- Investigators have direct access to the participant's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and reason for the unblinding must be fully documented in the case report form (CRF).

A participant may continue in the study if that participant's treatment assignment is unblinded.

GSK's GCSP staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

In addition, the bioanalytical laboratory, and pharmacy staff involved in preparation of SC administration syringes, will have access to the randomisation code. As there is a difference between active and placebo, where possible, administration syringes will be blinded by pharmacy staff using amber syringes or coloured, see through, tape to cover the full length of the syringe cylinder. If blinding isn't possible, participants will be dosed by independent staff, who will not be involved in any other procedures for any participant in a cohort that they dose.

Formal unblinded interim analyses will be performed by GSK (see Section 9.3.2).

6.4. Packaging and Labelling

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

6.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of GSK3511294 will be detailed in the Study Reference Manual (SRM), which will be accompanied by a Quality Agreement.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments 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 authorised site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose a significant safety risks to site staff. Adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists are advised.

In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.6. Compliance with Study Treatment Administration

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When participants are dosed with GSK3511294 subcutaneously at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and reported in the CRF. The dose of study treatment 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 treatment.

6.7. Treatment of Study Treatment Overdose

For this study, any dose of GSK3511294 greater than the specified dose for that cohort will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator should:

1. contact the Medical Monitor immediately
2. closely monitor the participant for AEs/ SAEs and laboratory abnormalities until GSK3511294 has reached a systemic level at a time point at which there were no safety concerns in previous participants
3. obtain a plasma sample for PK analysis within 4 weeks from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis). If beyond 4 weeks, then collect as soon as feasible

Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

6.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study. Mild to moderate asthmatics in this FTIH study aren't expected to benefit from GSK3511294. Other treatment options are available, and participants will remain on their standard of care during the study.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

6.9. Lifestyle and/or Dietary Restrictions

6.9.1. Meals and Dietary Restrictions

- Participants should arrive fasted for the screening visit only, and will be allowed to eat during the screening visit after blood draw for clinical chemistry has been completed.

6.9.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 6 hours prior to the visits that include a spirometry and/or ECG assessments, and during those visits.
- Participants will abstain from alcohol for 24 hours prior to each visit to the clinic and during the in-patient period.

6.9.3. Activity

- Participants will abstain from strenuous exercise for 72 hours prior to each blood collection for clinical laboratory tests.

6.9.4. Travel

- Participants must not have travelled to a country with a high prevalence of parasitic infections in the 6 months before screening, or intend to do so in the year after dosing.

6.10. Concomitant Medications and Non-Drug Therapies

6.10.1. Permitted Medications and Non-Drug Therapies

Paracetamol, at doses of ≤ 2 g/day, is permitted for use any time during the study. Hormone replacement therapy (HRT) is also permitted in females. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor. Special consideration should be given for those medications that might impact blood eosinophil counts.

The following asthmatic ‘standard of care’ will be used throughout the study, as prescribed by a treating physician.

- SABA i.e. albuterol, salbutamol prn. (Provided to participants in the form of ‘rescue medication’.)

AND

- ICS alone, or inhaled ICS/LABA combination. The ICS dose should be up to the maximum allowed daily dose (see Table 2) and stable for at least 12 weeks prior to study treatment.

Asthma medication will be temporarily withheld before spirometry assessments at screening and on Day –1: SABAs will be withheld for 6 hours; LABAs will be withheld for 12 hours; and LABAs with ultra-long activity will be withheld for 24 hours.

Given that participants have mild-moderate asthma and are controlled with stable therapy on entering the study, maintenance asthma therapy should remain unchanged for the duration of the study. In the event of asthma exacerbations, participants should however be treated as per standard practice, which may include short bursts of systemic corticosteroids. Any changes to maintenance asthma therapy should be documented and communicated to the sponsor.

6.10.2. Prohibited Medications and Non-Drug Therapies

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days or 5 half-lives (whichever is longer) prior to study medication administration and until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study. This excludes the background asthma standard of care defined in Section 6.10.1, which are permitted based on the established inclusion/exclusion criteria.

The following asthma medications are prohibited during the study and within the timeframe indicated in brackets before screening:

- Immunotherapy (at any time)
- Desensitization therapy (ongoing)
- anti-IgE therapy (within 6 months)
- anti-IL5 (within 6 months)
- oral or injectable corticosteroids (within 8 weeks)
- LAMA or LTRA therapy (within 8 weeks)
- Live vaccines

Medications that are known to prolong QT interval are also excluded. Some of the more commonly encountered drugs that are known to prolong QT interval are listed in Table 3.

Table 3 Drugs that can prolong the QT interval

Antimicrobials	Antipsychotics (all have some risk)	Antiarrhythmics	Antidepressants	Antiemetics	Others
Erythromycin Clarithromycin Moxifloxacin Fluconazole Ketoconazole	Risperidone Fluphenazine Haloperidol Pimozide Chlorpromazine Quetiapine Clozapine	Dronedarone Sotalol Quinidine Amiodarone Flecainide	Citalopram/ escitalopram Amitriptyline Clomipramine Dosulepin Doxepin Imipramine Lofepramine	Ondansetron/ Granisetron Droperidol Domperidone	Methadone Protein kinase inhibitors e.g. sunitinib Some antimalarials Some antiretrovirals Telaprevir Boceprevir

Notes: list taken from http://www.ggcprescribing.org.uk/media/uploads/ps_extra/pse_21.pdf.

Attenuated or non-live vaccines are prohibited within 5 days before and after dosing.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 7.1).

The following points must be noted:

- The timing and number of planned study assessments, including safety, PK, PD/biomarker, immunogenicity or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over any 3-month period during the study, including any extra assessments that may be required.

7.1. Time and Events Table

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Out-patient Visits [4,5]											
											Week											
											NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
											Day											
			Day –1	Day 1				Day 2	Day 3	Day 4	5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h												
Informed consent	X [6]																					
Pre-screening Blood eosinophils	X[7]																					
Inclusion & exclusion criteria		X	X	X																		
Demography	X																					
Medical history [10]		X																				
Concomitant medication		← →																				
HIV, Hep B and Hep C screen		X																				
FSH and estradiol [8]		X																				
Pregnancy test [9]		X	X											X	X	X	X	X		X [5]	X [5]	X [5]
Drug, alcohol and cotinine screen		X	X																			
Genetic sample					X [11]																	
Administer IP					X																	
ACT [12]		X													X		X			X [5]	X [5]	X [5]
Height, weight and BMI	X [13]		X [13]																	X [5,13]	X [5,13]	X [5,13]
Full phys exam		X																		X [5]	X [5]	X [5]
Brief phys exam			X			X				X		X			X							
Dispense rescue SABA		X	Resupply, as required.																			

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Out-patient Visits [4,5]											
				Day 1				Day 2	Day 3	Day 4	Week											
			Day –1	Pre-dose	0	2 h	8 h	24 h	48 h	72 h	NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
											Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Haematology (including blood eosinophil count), Clin. Chem., Urinalysis and hsCRP		X	X					X	X	X	X	X	X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Serum save (for immunological analysis, if needed)		X				Ad hoc, as required by symptoms – see Appendix 3.																
Inflammatory markers		X				Ad hoc, as required by symptoms – see Appendix 3.																
Complement (C3 & C4)		X	X					X	X	X	X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Total IgE			X					X	X	X	X			X	X	X	X	X		X [5]	X [5]	X [5]
PK Blood Samples				See Table 4.																		
Immunogenicity				X									X	X	X	X	X	X	X	X [5]	X [5]	X [5]
CICs				X				X					X	X	X	X	X	X	X	X [5]	X [5]	X [5]
12-lead ECG [14]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Vital signs [15]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [5]	X [5]	X [5]
AE/SAE review (inc local ISR up to 72 h after dosing)	X [16]		← →																			
IL-5 sample			X					X	X			X	X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Exploratory biomarkers of asthma in blood			X											X			X					
Spirometry		X	X			X		X		X		X			X					X [5]	X [5]	X [5]
PEF Training [17]		X																				
PEF [17]		X [17]																				
Diary review [17]											X	X	X	X	X	X	X	X	X	X [5]	X [5]	X [5]

Abbreviations: ACT = Asthma Control Test; AE = adverse event; BMI = body mass index; CICs = circulating immune complexes; CRP = C-reactive protein; ECG = electrocardiogram; FSH = follicle stimulating hormone; h = hour(s); Hep B = Hepatitis B; Hep C = Hepatitis C; HIV = human immunodeficiency virus; IgE = immunoglobulin E; IL-5 = interleukin-5; IP = Investigational Product; ISR = injection site reactions; PEF = peak expiratory flow; PK = pharmacokinetic; SABA = short acting β-agonist; SAE = serious adverse event.

Notes:

1. Pre-screen up to 12 weeks before dosing. Blood eosinophils must be ≥ 200 cells/μL for participants to proceed to screening. Blood eosinophil count may be existing data or obtained at a pre-screen visit.
2. Screening up to 4 weeks before randomisation. Screening procedures may be done at one or more visits, within the screening window.
3. In the UK, all participants will be in-patient for at least 72 h after dosing. In Germany, all participants will be in-patient for at least 8 days after dosing (see Appendix 8 for the German-specific time and events table).
4. Allowed time deviations will be documented in the Study Reference Manual.
5. All participants will have all out-patient visits up to Week 26 after dosing. Each cohort will also have out-patient visits after week 26, depending on the dose, as follows:
   - 2 and 10 mg: Week 32 only
   - 30 mg and 100 mg: Week 36 only
   - 300 mg: Weeks 32 and 40

   (For unplanned dose levels, the timing of out-patient visits will be documented in a Note to File.)
6. Informed consent will be taken either at the pre-screen visit, for participants who don't have an existing eosinophil count, or at screening, for those who do.
7. Blood eosinophils will be included in the haematology panel at all time points other than the pre-screen visit.
8. If required to confirm postmenopausal status.
9. Women on hormone replacement therapy, whose post-menopausal status cannot be confirmed, only.
10. Including cardiovascular (CV) disease, asthma exacerbation, and drug, alcohol and smoking history.
11. If the participant consents, an optional, genetic sample will be collected once during the study.
12. At each applicable visit, ACT should be done before any other assessment.
13. Height at pre-screening or screening only.
14. ECGs triplicate at all time points. ECGs should be time-matched to baseline (i.e. pre-dose on Day 1) from Day 2 onwards.
15. Blood pressure and heart rate in triplicate before dosing; single measurements after dosing. Single temperature and respiratory rate measurements at all time points.
16. Only SAEs are collected before dosing (see Section 7.3.1).
17. PEF will be recorded in the evening before bedtime on the day of the screening visit, then **twice** each day **(once in the morning upon waking and once in the evening before bedtime)** from the day after screening until the end of the study. Training of the participant in how to take measurements will occur at screening. PEF measurements will be taken and results will be recorded by the site while the participant is in-patient at the clinical site (ie from the evening of Day –1 until the morning of discharge). At all other time points, the participant will record their PEF as instructed, on their diary card, along with any rescue medication use and adverse events. Site staff will review the diary cards at each out-patient visit.

Table 4 Pharmacokinetic sampling time points

Dose level	Pre-dose	Post-dose															
		Hours				Days											
		2	8	24	48	5	8	15	29	57	85	127	169	183	225	253	281
2 mg and 10 mg	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
30 mg and 100 mg	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
300 mg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Notes: For unplanned dose levels, PK sampling time points will be documented in a Note to File.

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the participant's routine clinical management and obtained prior to signing of informed consent may be utilised for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Time and Events Schedule.

The Asthma Control Test (Appendix 7) should be completed by participants before any other assessment at a clinic visit, in the order specified.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 5.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., 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 up to dosing, and all SAEs will be documented after dosing, including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.1.3), at the time points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.

- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 5.

7.3.1.2. Method of Detecting AEs and SAEs

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

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.3.1.3. 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 AEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

7.3.1.4. Cardiovascular and Death Events

For any CV events detailed in Appendix 5 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

7.3.1.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and

ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.2. 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 the end of the mandated contraceptive period. If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

7.3.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Skin, Eyes and Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (screening only) 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

7.3.4. Vital Signs

- Vital signs will be measured in supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, heart rate and respiratory rate.

7.3.5. Electrocardiogram (ECG)

- 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.3.2 for QTc increased monitoring criteria and additional QTc readings that may be necessary.

The 12-lead ECG will be performed in the supine position. At all time points, after a 5 minutes rest, triplicate ECGs will be obtained over a brief recording period (up to

10 minutes). The ECGs will be time-matched to baseline assessment (ie pre-dose on Day 1) from Day 2 onwards. For QT interval corrected for heart rate (QTc), for the purposes of standardisation, Fridericia's correction formula (QTcF) was selected and will be used across sites with central over-read to limit variability.

7.3.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 5, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional, non-protocol specified, laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory, except for pre-screen eosinophils, which, if required, may be performed at the local laboratory.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed – for example: on Day –1, when results should be available before dosing on Day 1; at 48 h post-dose for all sentinel participants; at 48 h post-dose when results should be available before the participant is discharged from the clinical unit in the UK; on Day 8, when results should be available before the participant is discharged from the clinical unit in Germany; or at any other time when a participant is unwell and results are required urgently. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 5.

Table 5 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Haematology	Platelet Count; *RBC Indices*: MCV, MCH; *WBC count with Differential: (post-dose results blinded as described in footnote 1)*: WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils; RBC Count; Haemoglobin; Haematocrit
Clinical Chemistry	BUN; Creatinine; Glucose (fasted at screening); Potassium; Sodium; Calcium; Magnesium; AST (SGOT); ALT (SGPT); Alkaline phosphatase; Total and direct bilirubin; Total Protein; Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination and UACR (if blood or protein is abnormal [evidence of microalbuminuria or haematuria of ≥ 1+])
Other tests	• hsCRP
Other Screening Tests	• HIV • Hepatitis B (HBsAg; in Germany only, anti-HBc will also be tested [Appendix 8]) • Hepatitis C (Hep C antibody) • FSH and estradiol (if required to confirm postmenopausal status) • Alcohol, cotinine and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BUN = blood urea nitrogen; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; anti-HBc = hepatitis B core antibody; hsCRP = highly sensitive C-reactive protein; MCH = mean corpuscular haemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; UACR = urinary albumin-creatinine ratio; WBC = white blood cell, pH= hydrogen ion concentration.

1. The following post-dose results will be blinded to Investigators and blinded Sponsor representatives: total WBCs; absolute and percentage eosinophils; and percentage neutrophils, lymphocytes, monocytes and basophils.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within the defined in clinic follow up periods should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.3.7. Lung function tests

FEV_1, FVC and PEF will be measured, as described in the SRM.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

Blood samples for determination of GSK3511294 plasma concentration will be collected at the time points indicated in Table 4.

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the appropriate lab manual.

7.4.2. Sample Analysis

Plasma analysis will be performed under the control of Platform Technology and Science (PTS), GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of GSK3511294 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analysed for parent compound any remaining plasma may be analysed for other compound-related material and the results reported under a separate PTS, GlaxoSmithKline protocol.

7.5. Immunogenicity

Samples for testing binding antibodies against GSK3511294 will be collected at the time points indicated in the Time and Events Tables. The actual date and time of each blood sample collection will be recorded. Processing, storage and shipping procedures are provided in the SRM.

Sample analysis will be performed under the control of PTS, GlaxoSmithKline. The presence of anti-GSK3511294 binding antibodies will be determined in serum samples using a validated bioanalytical method, which includes a screening assay, confirmation assay and titre analysis. If necessary, further immune response characterization may be performed as needed.

7.6. Circulating Immune Complexes

Samples for circulating immune complexes (CIC) will be collected at the time points indicated in the Time and Events Tables. The actual date and time of each blood sample collection will be recorded. Processing, storage and shipping procedures are provided in the SRM.

Sample analysis will be performed under the control of PTS, GlaxoSmithKline. The presence of CICs will be determined in serum samples using a validated bioanalytical assay, using immunoglobulin detection. Further characterization with drug specific detection may be performed as needed.

7.7. Complement, IgE and inflammatory markers

Blood samples will be collected during the study to measure complement (C3 and C4) and total IgE. Assessments will be performed by a central laboratory.

Inflammatory markers at screening will comprise Tumour necrosis factor-alpha (TNF-α), IL-2, IL-6, IL-10, Interferon-gamma (IFN-γ) and C3a. A screening serum sample will also be stored for assay of Antinuclear antibodies (ANA), Anti-neutrophil cytoplasmic antibody (ANCA) and anti-DNA antibodies, if required at a later date based on symptoms. After dosing, additional inflammatory markers and tests will be considered on an ad hoc basis should there be clinical concerns regarding an immune mediated AE (see Section 5.4.2 and Appendix 3).

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

7.8. Pharmacodynamic and Exploratory Markers

7.8.1. Pharmacodynamic Biomarkers

Serum samples will be collected during this study to measure total IL-5 levels as a marker of target engagement. Additionally, blood eosinophil levels will be measured as part of the haematology panel as a marker of pharmacological response. Samples will be collected at the time points indicated in Section 7.1, Time and Events Tables. The timing of the collections may be adjusted on the basis of emerging PK or PD data from this study or other new information in order to ensure optimal evaluation of the biomarker endpoints.

7.8.2. Exploratory Biomarkers of Asthma

Serum samples will be collected during this study and may be used for the purposes of measuring biomarkers to identify factors that may influence the development of asthma and/or medically related conditions or the development of asthma treatments, as well as the biological and clinical responses to GSK3511294. Samples will be collected at the time points indicated in Section 7.1, Time and Events Table.

All exploratory biomarker samples will be retained for a maximum of 15 years after the last participant completes the trial.

7.9. Genetics

Information regarding genetic research is included in Appendix 4. Participant participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

8. DATA MANAGEMENT

- For this study participant data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- AEs and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSK Drug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Participant initials will not be collected or transmitted to GSK according to GSK policy.
- Participant initials and full date of birth will not be collected in the CRF or transmitted to GSK, according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

Given this study is the FTIH for GSK3511294, there are no formal statistical hypotheses to be tested. The assessment of safety and tolerability of single SC doses of GSK3511294 in this study will not include any formal comparisons. For the pharmacokinetic and pharmacodynamic data, where appropriate, an estimation approach will be adopted and point estimates with corresponding confidence intervals will be provided. In addition, for the analysis of blood eosinophils, posterior means and corresponding 95% credible intervals will be constructed for each dose and time point. Furthermore, posterior probabilities that the placebo adjusted ratio is less than various thresholds of interest will be constructed.

9.2. Sample Size Considerations

No formal statistical techniques were used to calculate the sample size for this study. The number of participants included is primarily determined by feasibility and is deemed an adequate number to provide an assessment of safety and tolerability, pharmacokinetics and pharmacodynamic measurements, and thereby to allow progression to larger clinical studies. More participants are planned in cohorts to be given doses in the expected therapeutic range to gain more information on those dose levels.

9.2.1. Sample Size Assumptions

Although the sample size is not based on statistical criteria, general probabilities can be determined on the likelihood of seeing adverse events. For example, with 6 participants receiving each dose of active drug, if the true adverse outcome rate is 5%, the chance of seeing at least one adverse outcome at a given dose is 26%. Similarly, if the true adverse

outcome rate is 20%, the chance of seeing at least one adverse outcome at a given dose is 74%. The corresponding figures for 9 participants with true event rates of 5% and 20% are 37% and 87%, respectively. This level of predictivity is deemed adequate within this FTIH setting, prior to progression to larger studies.

9.2.2. Sample Size Re-estimation or Adjustment

No formal sample size re-estimation will be performed. However, upon ongoing review of data, it is possible that the size of a cohort may be increased.

9.3. Data Analysis Considerations

Statistical analysis will be performed by, or under the direct auspices of Clinical Statistics, GlaxoSmithKline.

Complete details of the planned statistical analyses will be provided in the RAP.

9.3.1. Analysis Populations

For purposes of analysis, the following populations are defined:

- Screened: All participants who were screened.
- Safety: All randomised participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.
- Pharmacokinetic: Participants in the 'Safety' population for whom a pharmacokinetic sample was obtained and analysed.
- Pharmacodynamic: Participants in the 'Safety' population for whom a post-dose pharmacodynamic (i.e. blood eosinophil) sample was obtained and analysed.

9.3.2. Interim Analyses

In stream data review will occur during the study to support dose escalation decisions, and formal interim analyses are planned to ensure accumulated safety, PK and PD data are deemed sufficient to determine the doses and dosing interval to move forward into the next phase of development but is not expected to affect the progression of this FTIH study.

Currently, the first interim analysis is projected to occur once data is available at the 12-week time point after dosing in Cohort 4 (planned 100 mg dose). The primary focus of this interim analysis will be reduction in blood eosinophil counts. The ratio to baseline will be derived for each dose and time point and will be compared to corresponding data from the placebo arm. Posterior means and corresponding 95% credible intervals will be constructed for each of the available doses and time points. Furthermore, posterior probabilities that the placebo adjusted ratio is less than various thresholds of interest will be constructed.

The earliest next interim analysis is planned no earlier than once data is available at the 26-week time point after dosing Cohort 4 (planned 100 mg dose). The primary focus of

this and potential subsequent interim analyses will be the same as the first interim analysis (described above).

The interim analyses will be performed by GSK Clinical Statistics and only the responsible statistician (and Quality control [QC] statistician) and the CPMS representative will have access to individual participant data. However, the findings of the interim analyses will be shared with the entire GSK study team.

9.4. Key Elements of Analysis Plan

On-going PK analyses will be performed on plasma concentration-time data available prior to dose escalation decisions in subsequent cohorts.

For these on-going analyses, plasma concentration-time data will be analysed by non-compartmental methods using nominal times. The decision to proceed to higher doses will be made by the Dose Escalation Committee based on assessment of safety/tolerability and PK data at lower dose levels, together with any available PD data if deemed appropriate.

9.4.1. Primary Analyses

All safety analyses will be performed on the Safety Population. Safety data will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.4.2. Secondary Analyses

All pharmacokinetic analyses will be conducted on the Pharmacokinetic Population.

9.4.2.1. Raw Plasma PK Concentrations

Blood sampling time will be related to the start of dosing. Linear and semi-logarithmic individual plasma concentration-time profiles and mean and median profiles by GSK3511294 dose will be plotted. Plasma concentrations of GSK3511294 will be listed and summarised by dose and nominal time.

9.4.2.2. Derived Plasma Pharmacokinetic Parameters

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, QSci, GSK. Plasma concentration-time data for GSK3511294 will be analysed by non-compartmental methods according to GlaxoSmithKline guidance document, GUI_00000051487 and using 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
- Vd/F
- λz
- the number of points used to determine λz
- t1/2

Pharmacokinetic data will be presented in graphical and/or tabular form and will be listed and summarised descriptively by treatment 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 Clinical Statistics, GlaxoSmithKline.

Assessment of Dose Proportionality

An initial assessment of dose proportionality will be explored for AUC(0-∞) and Cmax following single SC doses of GSK3511294 using graphical presentations, if data permits. Further exploratory statistical analysis to assess dose proportionality may be performed, to be detailed in the Reporting Analysis Plan (RAP).

9.4.2.3. Blood eosinophil count

Blood eosinophil count will be log transformed prior to analysis and the ratio to baseline for each dose and time point will be summarised using appropriate descriptive statistics and will be compared to corresponding data from the placebo arm. The primary intent will be to analyse this data by fitting a Bayesian dose response model. The 4-parameter Emax model will be fitted by first intent; however, should the data not allow for a suitable model fit, then other models may be attempted. Posterior means and corresponding 95% credible intervals will be constructed for each dose and time point. Furthermore, posterior probabilities that the placebo adjusted ratio is less than various thresholds of interest will be constructed.

9.4.3. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between plasma concentration and blood eosinophil count after single subcutaneous doses of GSK3511294 will be explored, if data permits, by population PK methods using for example an indirect response model. Full details of the analysis to be performed will be provided in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of participants begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH GCP, all applicable participant privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favourable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained and available for each participant prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of participants are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicentre studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the

opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis. The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACT	Asthma Control Test
ADA	Anti-drug antibody
AE	Adverse Event
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
APTT	Activated partial thromboplastin time
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
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CIC	Circulating immune complex
CFC	Chorofluorocarbonate
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
Ctrough	Lowest concentration of a drug just before the next dose
CV	Cardiovascular
DEC	Dose Escalation Committee
DNA	Deoxyribonucleic acid
DPI	Dry Powder inhaler
EC50	Half maximal effective concentration
ECG	Electrocardiogram

eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ESR	Erythrocyte sedimentation rate
FAAN	Food Allergy and Anaphylaxis Network
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FTIH	First Time in Humans
FVC	Forced vital capacity
g	Grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
h	Hours
HBsAg	Hepatitis B Surface Antigen
HFA	Hydrofluoroalkane propellant
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HRT	Hormone replacement therapy
hsCRP	High sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IgG1	Immunoglobulin G1
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IL	Interleukin
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ISR	Injection site reactions
IV	Intravenous
kDa	kilodalton
kg	kilogram
L	Litre
LABA	Long acting β-agonist
LAMA	Long acting muscarinic antagonist
LAMBDAz	Terminal phase rate constant
LDH	Lactate dehydrogenase
LTRA	Leukotriene receptor antagonist

mAb	Monoclonal antibody
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
mm Hg	Millimetre of mercury
mol	Mole
MSDS	Material Safety Data Sheet
msec	Milliseconds
NIAID	National Institute of Allergy and Infectious Disease
NOAEL	No Observed Adverse Effect Level
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PEF	Peak expiratory flow
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
SABA	Short acting β-agonist
SAE	Serious Adverse Event
SC	Subcutaneous
SGPT	Serum glutamic pyruvic transaminase
SGOT	Serum glutamic oxaloacetic transaminase
SRM	Study Reference Manual
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
TK	Toxicokinetics
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
Vd/F	Apparent volume of distribution after subcutaneous administration
WBC	White blood cell
W/V	Weight/volume
µL	Microlitre

Trademark Information

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12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Liver chemistry increased monitoring criteria and required follow up assessments

Liver Chemistry Increased Monitoring Criteria	
ALT-absolute	ALT≥3xULN If ALT≥3xULN **AND bilirubin**[1,2] ≥ 2xULN (>35% direct bilirubin) or **INR** >1.5, Report as an SAE. See additional Actions and Follow Up Assessments listed below

Required Actions and Follow up Assessments following Liver Event	
Actions	**Follow Up Assessments**
• Report the event to GSK **within 24 hours** • Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below)	• Viral hepatitis serology[3] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, obtained within a week of meeting increased liver monitoring criteria[4] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • 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. Investigators should be blinded to those results, unless unblinding is required for participant safety. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including

	acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form
MONITORING: **<u>If</u> ALT≥3xULN AND <u>bilirubin ≥</u> 2xULN <u>or INR</u> >1.5<u>:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hours** • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **<u>If</u> ALT≥3xULN <u>AND bilirubin</u> < 2xULN <u>and INR</u> ≤1.5<u>:</u>** **1.** Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hours** • Monitor participants weekly until liver chemistries resolve, stabilise or return to within baseline	**<u>If</u> ALT≥3xULN AND <u>bilirubin ≥</u> 2xULN <u>or INR</u> >1.5<u>:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct High-performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); 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. PK sample may not be required for participants known to be receiving placebo. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If 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 appropriate lab manual.

12.2.1. References

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

12.3. Appendix 3: Investigations and management in the event of immune related adverse events or relevant clinical concern

The early recognition of immune-related AEs and initiation of treatment are important in reducing the clinical impact, as the majority of these AEs are reversible with the use of steroids and other immunosuppressants; however, the symptoms and clinical features are often non-specific and heterogenous in regards to the time course over which they develop, organ involvement and indeed the constellation of symptoms and severity. 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 adverse events, these factors should be given due consideration and ruled out, especially as infection may be at risk of deterioration with empirical immunosuppression.

If an immune-related AE is suspected, the participant should contact the study site as soon as possible, instead of waiting for his/her next scheduled visit. A thorough evaluation should be conducted in an effort to properly diagnose an immune-related AE and rule out other potential causes (infectious, neoplastic, metabolic, toxic). 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.

PK, ADA and CIC samples will be taken at the time of the event and samples will be taken for additional biomarkers in the setting of clinical concern regarding the possibility of immune complex disease; suggested additional samples will comprise coagulation parameters (Activated partial thromboplastin time [APTT] and INR), Erythrocyte sedimentation rate (ESR) and C3a, should there be clinical features as indicated in Section 5.4.2. Furthermore, samples for ANA, ANCA and anti-DNA antibodies will be taken as biomarkers of autoimmune disease and these same antibodies will be measured on frozen serum samples taken and stored before dosing to identify any interval change. Other possible causative or differential factors for abnormal clinical or laboratory observations will also be investigated including testing to exclude infection. Suspected immune complex disease should be reported as an AE or SAE, whichever appropriate, within 24 hours as indicated in Section 5.4.2.

Where no alternative cause is established in the setting of inflammatory signs and/ or symptoms, or there be ongoing clinical concern, the patient will be referred to a specialist for further management. In the setting of clinically relevant pathology, target organ biopsy should be considered after consultation with an appropriate clinical specialist. Specifically, given the relative ease of performing a skin biopsy, if a rash is observed, consultation with a dermatologist with a view to performing skin biopsies should be considered.

12.4. Appendix 4: Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including GSK3511294 or any concomitant medicines;
- Asthma susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilise data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a RAP prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any participant who is enrolled in the study can participate in genetic research. Any participant who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been

identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for DNA extraction. A blood sample is collected after the participant has been dosed and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilise the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the participant by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last participant completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Participants can request their sample to be destroyed at any time.

Informed Consent

Participants who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Participant Withdrawal from Study

If a participant who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the participant will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a participant withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analysed during the study or stored for future analysis.

- If a participant withdraws consent for genetic research and genotype data has not been analysed, it will not be analysed or used for future research.
- Genetic data that has been analysed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Provision of Study Results and Confidentiality of Participant's Genetic Data

GSK may summarise the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the participant, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the participant's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

Reference

Chen H, Yu K-D, Xu G-Z. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. *PLOS ONE*. 2012;7:e42464.

Gorin MB. Genetic insights into age-related macular degeneration: controversies addressing risk, causality, and therapeutics. *Mol Aspects Med*. 2012;33:467-86.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: 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 a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• 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 an AE. • Situations where 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.

12.5.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

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 hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils 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 disability/incapacity

NOTE:

- 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, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury and impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

- Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.5.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.5.4. Recording of AEs and SAEs

AEs 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) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Participant-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.5.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will 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 is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of 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 when 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 prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable, the site will use the paper SAE data collection tool in order to report the event within 24 hours and fax it to the Medical Monitor • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the Electronic case report form (eCRF) page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) 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, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator] by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: Modified List of Highly Effective Methods of Contraception for post-menopausal females, who are taking Hormone Replacement Therapy, and Collection of Pregnancy Information

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 required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Post-menopausal females, under 60 years of age, who are taking HRT and have not had their menopausal status confirmed, must use one of the follow methods of contraception, from dosing until the final visit.

1. Male partner sterilization with documentation of azoospermia prior to the female participant's entry into the study, and this male is the sole partner for that participant [Hatcher, 2011]. The documentation on male sterility can come from the site

personnel's: review of participant's medical records or medical history interview provided by her or her partner.

The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating will continue to attend all follow-up visits.

12.6.1. References

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

12.7. Appendix 7: Asthma Control Test

Country-specific, commercially available versions of the ACT will be used.

12.8. Appendix 8: Country Specific Requirements

12.8.1. Additional Hepatitis B Core Antibody test for inclusion of participants in Germany

In order to comply with German requirements for Hepatitis B virus testing in Germany, participants will be tested for the hepatitis B core antibody (anti-HBc) at screening. The German-specific exclusion criterion 5 is as follows:

Positive for **hepatitis B** surface antigen (HBsAg) and core antibody (anti-HBc) at screening.

Table 5 has been updated accordingly.

12.8.2. Additional In-patient stay period for participants from Germany

In Germany, participants will remain in-patient for a minimum of 8 days post dosing, as noted in Section 4.2, Section 4.7.1, Section 7.1. For clarity, the time and events table for Germany is provided below.

12.8.2.1. Time and Events Table

Procedure	Pre-Screen [1]	Screen [2]	In-patient Period [3,4]								Out-patient Visits [4,5]													
											Week													
				Day 1				Day 2	Day 3	Day 4	NA	1	NA	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
			Day –1	Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day													
											5	8	9	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]	
Informed consent	X [6]																							
Pre-screening Blood eosinophils	X [7]																							
Inclusion & exclusion criteria		X	X	X																				
Demography	X																							
Medical history [10]		X																						
Concomitant medication		◄———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———►
HIV, Hep B and Hep C screen		X																						
FSH and estradiol [8]		X																						
Pregnancy test [9]		X	X												X	X	X	X	X		X [5]	X [5]	X [5]	
Drug, alcohol and cotinine screen		X	X																					
Genetic sample					X [11]																			
Administer IP					X																			
ACT [12]		X														X		X			X [5]	X [5]	X [5]	
Height, weight and BMI	X [13]		X [13]																		X [5,13]	X [5,13]	X [5,13]	
Full phys exam		X														X					X [5]	X [5]	X [5]	
Brief phys exam			X			X				X		X				X								
Dispense rescue SABA		X	Resupply, as required.																					

Procedure	Pre-Screen [1]	Screen [2]	In-patient Period [3,4]								Out-patient Visits [4,5]												
				Day 1				Day 2	Day 3	Day 4	Week												
											NA	1	NA	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
			Day –1	Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day												
											5	8	9	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Haematology (including blood eosinophil count), Clin. Chem., Urinalysis and hsCRP		X	X					X	X	X	X	X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Serum save (for immunological analysis, if needed)		X				Ad hoc, as required by symptoms – see Appendix 3.																	
Inflammatory markers		X				Ad hoc, as required by symptoms – see Appendix 3.																	
Complement (C3 & C4)		X	X					X	X	X	X			X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Total IgE			X					X	X	X	X				X	X	X	X	X		X [5]	X [5]	X [5]
PK Blood Samples				See Table 4.																			
Immunogenicity				X										X	X	X	X	X	X	X	X [5]	X [5]	X [5]
CICs				X				X						X	X	X	X	X	X	X	X [5]	X [5]	X [5]
12-lead ECG [14]		X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Vital signs [15]		X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]
AE/SAE review (inc local ISR up to 72 h after dosing)	X [16]			←																			→
IL-5 sample			X					X	X			X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Exploratory biomarkers of asthma in blood			X												X			X					
Spirometry		X	X			X		X		X		X				X					X [5]	X [5]	X [5]
PEF Training [17]		X																					

Procedure	Pre-Screen [1]	Screen [2]	In-patient Period [3,4]								Out-patient Visits [4,5]												
											Week												
											NA	1	NA	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
			Day –1	Day 1				Day 2	Day 3	Day 4	Day												
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	5	8	9	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
PEF [17]		X [17]																					
Diary review [17]											X	X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]

Abbreviations: ACT = Asthma Control Test; AE = adverse event; BMI = body mass index; CICs = circulating immune complexes; CRP = C-reactive protein; ECG = electrocardiogram; FSH = follicle stimulating hormone; h = hour(s); Hep B = Hepatitis B; Hep C = Hepatitis C; HIV = human immunodeficiency virus; IgE = immunoglobulin E; IL-5 = interleukin-5; IP = Investigational Product; ISR = injection site reactions; PEF = peak expiratory flow; PK = pharmacokinetic; SABA = short acting β-agonist; SAE = serious adverse event.

Notes:

1. Pre-screen up to 12 weeks before dosing. Blood eosinophils must be ≥ 200 cells/μL for participants to proceed to screening. Blood eosinophil count may be existing data or obtained at a pre-screen visit.
2. Screening up to 4 weeks before randomisation. Screening procedures may be done at one or more visits, within the screening window.
3. All participants will be in-patient for at least 8 days after dosing.
4. Allowed time deviations will be documented in the Study Reference Manual.
5. All participants will have all out-patient visits up to Week 26 after dosing. Each cohort will also have out-patient visits after week 26, depending on the dose, as follows:
   - 2 and 10 mg: Week 32 only
   - 30 mg and 100 mg: Week 36 only
   - 300 mg: Weeks 32 and 40

   (For unplanned dose levels, the timing of out-patient visits will be documented in a Note to File.)
6. Informed consent will be taken either at the pre-screen visit, for participants who don't have an existing eosinophil count, or at screening, for those who do.
7. Blood eosinophils will be included in the haematology panel at all time points other than the pre-screen visit.
8. If required to confirm postmenopausal status.
9. Women on hormone replacement therapy, whose post-menopausal status cannot be confirmed, only.
10. Including cardiovascular (CV) disease, asthma exacerbation, and drug, alcohol and smoking history.
11. If the participant consents, an optional, genetic sample will be collected once during the study.
12. At each applicable visit, ACT should be done before any other assessment.
13. Height at pre-screening or screening only.
14. ECGs triplicate at all time points. ECGs should be time-matched to baseline (i.e. pre-dose on Day 1) from Day 2 onwards.
15. Blood pressure and heart rate in triplicate before dosing; single measurements after dosing. Single temperature and respiratory rate measurements at all time points.
16. Only SAEs are collected before dosing (see Section 7.3.1).

17. PEF will be recorded in the evening before bedtime on the day of the screening visit, then **twice** each day **(once in the morning upon waking and once in the evening before bedtime)** from the day after screening until the end of the study. Training of the participant in how to take measurements will occur at screening. PEF measurements will be taken and results will be recorded by the site while the participant is in-patient at the clinical site (ie from the evening of Day –1 until the morning of discharge). At all other time points, the participant will record their PEF as instructed, on their diary card, along with any rescue medication use and adverse events. Site staff will review the diary cards at each out-patient Visit.

12.9. Appendix 9: 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 lipstongue-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) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

12.9.1. References

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson Jr NF, Bock SA, Branum A et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-397.

12.10. Appendix 10: Protocol Changes

12.10.1. Protocol Amendment 1

Protocol Amendment 1 applies to all sites.

Description of changes

Change 1: Medical Monitor/SAE Contact Information: Secondary Medical Monitor

Change from:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Secondary Medical Monitor	PPD	PPD	PPD		GSK Gunnels Wood Road Stevenage Hertfordshire SG1 2NY UK

To:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Secondary Medical Monitor	PPD	PPD	PPD		GSK Gunnels Wood Road Stevenage Hertfordshire SG1 2NY UK

Rationale: to correct the secondary Medical Monitor's email address

Change 2: Section 7.1, Time and Events Table, Inflammatory markers sample collection row

Change from:

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Outpatient Visits [4,5]											
				Day 1				Day 2	Day 3	Day 4	Week											
											NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
			Day –1	Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Inflammatory markers		X				Ad hoc, as required by symptoms – see Appendix 3.																

To:

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Outpatient Visits [4,5]											
				Day 1				Day 2	Day 3	Day 4	Week											
											NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
			Day –1	Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Serum save (for immunological analysis, if needed)		**X**				**Ad hoc, as required by symptoms – see Appendix 3**.																
Inflammatory markers		X				Ad hoc, as required by symptoms – see Appendix 3.																

Rationale: to clarify blood sampling needed for inflammatory markers

Change 3: Section 7.7, Complement, IgE and inflammatory markers, Paragraph 2

Change from:

Inflamatory markers at screening will comprise Tumour necrosis factor-alpha (TNF-α), IL-2, IL-6, IL-10, Interferon-gamma (IFN-γ)~~,~~ C3a~~/C3d~~, Antinuclear antibodies (ANA), Anti-neutrophil cytoplasmic antibody (ANCA) and anti-DNA antibodies. After dosing, additional inflammatory markers and tests will be considered on an ad hoc basis should there be clinical concerns regarding an immune mediated AE (see Section 5.4.2 and Appendix 3).

To:

Inflamatory markers at screening will comprise Tumour necrosis factor-alpha (TNF-α), IL-2, IL-6, IL-10, Interferon-gamma (IFN-γ) **and** C3a**. A screening serum sample will also be stored for assay of** Antinuclear antibodies (ANA), Anti-neutrophil cytoplasmic antibody (ANCA) and anti-DNA antibodies**, if required at a later date based on symptoms**. After dosing, additional inflammatory markers and tests will be considered on an ad hoc basis should there be clinical concerns regarding an immune mediated AE (see Section 5.4.2 and Appendix 3).

Rationale: to correct the markers to be measured at screening and those for which samples will be taken and stored for analysis later in the study, if required

12.10.2. Protocol Amendment 2

Protocol Amendment 2 applies to all sites.

Description of changes

Change 1: Section 4.3, Dose Escalation, PK stopping criterion

Change from:

- The dose will be increased only if safety and tolerability at previous dose levels are acceptable, and also if the predicted exposure (~~mean~~ C_{max} and ~~mean~~ AUC) at the next dose level does not exceed exposure observed at the NOAEL in monkey in the 26 week toxicity study (100 mg/kg).

mean C_{max}: 1390 µg/mL	mean $AUC_{0–2016}$ 1120000 µg.h/mL

To:

- The dose will be increased only if safety and tolerability at previous dose levels are acceptable, and also if the predicted exposure (**upper 95% prediction interval for** C_{max} and AUC) at the next dose level does not exceed **the mean** exposure observed at the NOAEL in monkey in the 26 week toxicity study (100 mg/kg).

mean C_{max}: 1390 µg/mL	mean $AUC_{0–2016}$ 1120000 µg.h/mL

Rationale: the MHRA commented that the use of mean PK data for a stopping criterion is unacceptable and this should be amended in the protocol to the maximum clinical exposure in an individual subject. As the study is using a parallel design, it is not possible to predict the exposure (Cmax and AUC) at the next dose level for a particular individual, so the upper 95% prediction interval at the next dose was used instead.

Change 2: Section 6.1, Investigational Product and Other Study Treatment, Study treatment table, Manufacturer/Source of procurement row

Change from:

	Study Treatment	
Product name:	**GSK3511294 Injection, 150 mg/mL**	**0.9% w/v Sodium Chloride Injection (placebo)**
Manufacturer/ Source of procurement:	GSK	~~Provided~~ by trial site

To:

	Study Treatment	
Product name:	**GSK3511294 Injection, 150 mg/mL**	**0.9% w/v Sodium Chloride Injection (placebo)**
Manufacturer/ Source of procurement:	GSK	**Locally sourced** by trial site

Rationale: to clarify that saline for placebo will be an EU licensed product sourced locally by sites.

12.10.3. Protocol Amendment 3 – Protocol changes for Amendment 03 (04-SEP-2017), from amendment 02 (04-Aug-2017)

Protocol Amendment 3 applies to all sites.

Description of changes

Change 1: Synopsis, Rationale

Change from:

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 severe eosinophilic asthma, as an add-on treatment administered every 4 weeks. GSK3511294 is expected to confer efficacy over a dosing interval of up to 6 months. This single ascending dose first time in humans (FTIH) study will investigate safety, tolerability, immunogenicity, pharmacokinetics (PK) and pharmacodynamics (PD) of GSK3511294, administered subcutaneously in participants with mild to moderate asthma maintained on a low–medium daily dose of inhaled corticosteroids (ICS) or ICS/long

acting β-agonist (LABA), and short acting β-agonist (SABA).~~.~~ To facilitate the investigation of blood eosinophil counts following single doses of GSK3511294, eligible participants will have a blood eosinophil count of ≥ 200 cells/μL at screening. This should enable a quantification of the prolonged blood eosinophil reduction that is anticipated in humans resulting from the combination of the extended half-life and greater affinity to IL-5 of GSK3511294.

To:

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 severe eosinophilic asthma, as an add-on treatment administered every 4 weeks. GSK3511294 is expected to confer efficacy over a dosing interval of up to 6 months. This single ascending dose first time in humans (FTIH) study will investigate safety, tolerability, immunogenicity, pharmacokinetics (PK) and pharmacodynamics (PD) of GSK3511294, administered subcutaneously in participants with mild to moderate asthma maintained on a low–medium daily dose of inhaled corticosteroids (ICS) or ICS/long acting β-agonist (LABA), and short acting β-agonist (SABA). To facilitate the investigation of blood eosinophil counts following single doses of GSK3511294, eligible participants will have a blood eosinophil count of ≥ 200 cells/μL at screening. This should enable a quantification of the prolonged blood eosinophil reduction that is anticipated in humans resulting from the combination of the extended half-life and greater affinity to IL-5 of GSK3511294.

Rationale: to correct a typographical error.

Change 2: Synopsis, Treatment Arms and Duration

Change from:

- Blood eosinophils pre-screen and screening: a blood eosinophils pre-screen assessment will be performed. Participants are eligible to skip the blood eosinophils pre-screening visit and go directly to the screening visit, if they have a documented blood test result within 12 weeks before ~~screening~~ demonstrating a blood eosinophil level ≥ 200 cells/μL. Participants who fulfil the pre-screening criteria will then attend the clinic for a full screening visit. Blood eosinophil level will be measured at screening to confirm eligibility.

To:

- Blood eosinophils pre-screen and screening: a blood eosinophils pre-screen assessment will be performed. Participants are eligible to skip the blood eosinophils pre-screening visit and go directly to the screening visit, if they have a documented blood test result within 12 weeks before **dosing** demonstrating a blood eosinophil level ≥ 200 cells/μL. Participants who fulfil the pre-screening criteria will then attend

the clinic for a full screening visit. Blood eosinophil level will be measured at screening to confirm eligibility.

Rationale: to correct an error.

Change 3: Section 4.2, Treatment Arms and Duration

Change from:

- Blood eosinophils pre-screen and screening: It is anticipated that a high proportion of the defined asthma population may have blood eosinophil levels that do not meet the inclusion criteria of ≥ 200 eosinophil cells/μL, therefore a blood eosinophils pre-screen assessment will be performed. Participants are eligible to skip the blood eosinophils pre-screening visit and go directly to the screening visit, if they have a documented blood test result within 12 weeks before ~~screening~~ demonstrating a blood eosinophil level ≥ 200 cells/μL. If blood eosinophil levels within the prior 12 weeks are not available, participants will provide written informed consent at a pre-screening visit followed by a pre-screen assessment of blood eosinophil level. Participants who fulfil the pre-screening criteria will then attend the clinic for a full screening visit. Blood eosinophil level will be measured at screening to confirm eligibility.

To:

- Blood eosinophils pre-screen and screening: It is anticipated that a high proportion of the defined asthma population may have blood eosinophil levels that do not meet the inclusion criteria of ≥ 200 eosinophil cells/μL, therefore a blood eosinophils pre-screen assessment will be performed. Participants are eligible to skip the blood eosinophils pre-screening visit and go directly to the screening visit, if they have a documented blood test result within 12 weeks before **dosing** demonstrating a blood eosinophil level ≥ 200 cells/μL. If blood eosinophil levels within the prior 12 weeks are not available, participants will provide written informed consent at a pre-screening visit followed by a pre-screen assessment of blood eosinophil level. Participants who fulfil the pre-screening criteria will then attend the clinic for a full screening visit. Blood eosinophil level will be measured at screening to confirm eligibility.

Rationale: to correct an error.

Change 4: Section 5.4.2, Criteria for follow up of potential Type III Hypersensitivity/ Immune Complex Disease

Change from:

- urinary albumin-creatinine ratio > 3 mg/mol in the absence of a urinary tract infection

To:

- urinary albumin-creatinine ratio > 3 mg/**m**mol in the absence of a urinary tract infection

Rationale: to correct an error in the units for urinary albumin-creatinine ratio.

Change 5: Section 5.4.3.2, QTc criteria for increased monitoring of individual participants

Change from:

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

- QT or QTc change from baseline ≥ 60 msec and no clinical impact. (Baseline is the average of ~~triplcaite~~ readings at pre-dose on Day 1.)
- QTc > 500 msec or uncorrected QT > 600 msec and no clinical impact.

***** To remain under observation if QT/QTc remains the same/increases on assessment at 24 (end of direct observation) and 72 hours periods (after 48 hour Holter monitor) and for consideration of cardiology consult.

For participants with underlying **bundle-branch block**, follow the evaluation criteria listed below:

- Baseline < 450 msec, increase monitoring at > 500 msec
- Baseline between 450 to 480 msec, increase monitoring at ≥ 530 msec

To:

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

- QT or QTc change from baseline ≥ 60 msec and no clinical impact. (Baseline is the average of **triplicate** readings at pre-dose on Day 1.)
- QTc > 500 msec or uncorrected QT > 600 msec and no clinical impact.

***** To remain under observation if QT/QTc remains the same/increases on assessment at 24 (end of direct observation) and 72 hours periods (after 48 hour Holter monitor) and for consideration of cardiology consult.

For participants with underlying **bundle-branch block**, follow the evaluation criteria listed below:

- Baseline **QTc** < 450 msec, increase monitoring at **QTc** > 500 msec
- Baseline **QTc** between 450 to 480 msec, increase monitoring at **QTc** ≥ 530 msec

Rationale: to correct a spelling mistake and clarify that evaluation criteria relate to QTc.

Change 6: Section 6.5, Investigational Product Preparation/Handling/Storage/ Accountability

Change from:

A description of the methods and materials required for preparation of GSK3511294 will be detailed in ~~a Study Specific Technical Agreement/Memo (TTS) or Pharmacy Manual~~ which will be accompanied by a Quality Agreement.

- Further guidance and information for final disposition of unused study treatment are provided in the ~~Study Reference Manual (~~SRM~~)~~.

To:

A description of the methods and materials required for preparation of GSK3511294 will be detailed in **the Study Reference Manual (SRM),** which will be accompanied by a Quality Agreement.

- Further guidance and information for final disposition of unused study treatment are provided in the SRM.

Rationale: to correct an error.

Change 7: Section 6.10.1, Permitted medications and non-drug therapies

Change from:

Asthma medication will be temporarily withheld before the reversibility test at screening, and spirometry assessments on Day –1: SABAs will be withheld for 6 hours; LABAs will be withheld for 12 hours; and LABAs with ultra-long activity will be withheld for 24 hours.

To:

Asthma medication will be temporarily withheld before the reversibility test at **pre-screening or** screening, and spirometry assessments **at screening and** on Day –1: SABAs will be withheld for 6 hours; LABAs will be withheld for 12 hours; and LABAs with ultra-long activity will be withheld for 24 hours.

Given that participants have mild-moderate asthma and are controlled with stable therapy on entering the study, maintenance asthma therapy should remain unchanged for the duration of the study. In the event of asthma exacerbations, participants should however be treated as per standard practice, which may include short bursts of systemic corticosteroids. Any changes to maintenance asthma therapy should be documented and communicated to the sponsor.

Rationale: to clarify rescue medication restrictions in relation to reversibility testing and spirometry, and to account for treatment of possible asthma exacerbations and to ensure that any changes in maintenance asthma therapy during the study are documented and communicated to the sponsor. The latter is because asthma exacerbations and changes in asthma therapy could affect the PD results.

Change 8: Section 7.1, Time and Events Table, Spirometry and PEF rows, and footnotes 2 and 18

Change from:

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Outpatient Visits [4,5]											
				Day 1				Day 2	Day 3	Day 4	Week											
											NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
											Day											
			Day −1	Pre-dose	0	2 h	8 h	24 h	48 h	72 h	5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Spirometry			X			X		X		X		X			X					X [5]	X [5]	X [5]
PEF [18]			~~X~~	~~X~~				~~X~~	~~X~~	~~X~~	X [18]											

2. Screening up to 4 week before randomisation. Screening procedures may be done at one or more visits, within the screening window.

18. PEF will be recorded each day during the study from Day −1 onwards. On Days −1 to 3, results will be recorded by the site; on all other days, results will be recorded by the participant, along with any rescue medication use, on diary cards provided by the site. Site staff will review the diary cards at each outpatient visit.

To:

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Outpatient Visits [4,5]											
				Day 1				Day 2	Day 3	Day 4	Week											
											NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
											Day											
			Day −1	Pre-dose	0	2 h	8 h	24 h	48 h	72 h	5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Spirometry		**X**	X			X		X		X		X			X					X [5]	X [5]	X [5]
PEF [18]			X [18]																			

2. Screening up to 4 week**s** before randomisation. Screening procedures may be done at one or more visits, within the screening window.

18. PEF will be recorded **twice** each day **(once in the morning upon waking and once in the evening before bedtime)** during the study from Day −1 onwards. On Days −1 to 3, results will be recorded by the site; on all other days, results will be recorded by the participant, along with any rescue medication use, on diary cards provided by the site. Site staff will review the diary cards at each outpatient visit.

Rationale: to correct a typographical error and to clarify that spirometry will be done at screening, in line with the study eligibility criteria, and that PEF should be measured twice daily.

Change 9: Section 7.7, Complement, IgE and inflammatory markers

Change from:

~~Inflamatory~~ markers at screening will comprise Tumour necrosis factor-alpha (TNF α), IL 2, IL 6, IL 10, Interferon-gamma (IFN γ) and C3a. A screening serum sample will also be stored for assay of Antinuclear antibodies (ANA), Anti-neutrophil cytoplasmic antibody (ANCA) and anti-DNA antibodies, if required at a later date based on symptoms. After dosing, additional inflammatory markers and tests will be considered on an ad hoc basis should there be clinical concerns regarding an immune mediated AE (see Section 5.4.2 and Appendix 3).

To:

Inflammatory markers at screening will comprise Tumour necrosis factor-alpha (TNF α), IL 2, IL 6, IL 10, Interferon-gamma (IFN γ) and C3a. A screening serum sample will also be stored for assay of Antinuclear antibodies (ANA), Anti-neutrophil cytoplasmic antibody (ANCA) and anti-DNA antibodies, if required at a later date based on symptoms. After dosing, additional inflammatory markers and tests will be considered on an ad hoc basis should there be clinical concerns regarding an immune mediated AE (see Section 5.4.2 and Appendix 3).

Rationale: to correct a typographical error.

Change 10: Section 9.1, Hypotheses

Change from:

Given this study is the FTIH for GSK3511294, there are no formal statistical hypotheses to be tested. The assessment of safety and tolerability of single SC doses of GSK3511294 in this study will not include any formal comparisons. For the pharmacokinetic and pharmacodynamic data, where appropriate, an estimation approach will be adopted and point estimates with corresponding confidence intervals will be provided. In addition for the analysis of blood ~~esoinophils~~, posterior means and corresponding 95% credible intervals will be constructed for each dose and time point. Furthermore, posterior probabilities that the placebo adjusted ratio is less than various thresholds of interest will be constructed.

To:

Given this study is the FTIH for GSK3511294, there are no formal statistical hypotheses to be tested. The assessment of safety and tolerability of single SC doses of GSK3511294 in this study will not include any formal comparisons. For the pharmacokinetic and pharmacodynamic data, where appropriate, an estimation approach will be adopted and point estimates with corresponding confidence intervals will be

provided. In addition for the analysis of blood **eosinophils**, posterior means and corresponding 95% credible intervals will be constructed for each dose and time point. Furthermore, posterior probabilities that the placebo adjusted ratio is less than various thresholds of interest will be constructed.

Rationale: to correct a typographical error.

Change 11: Section 9.3.2, Interim analysis

Change from:

The interim analysis will be performed by GSK Clinical Statistics and only the responsible statistician (and Quality ~~contol~~ [QC] statistician) and the CPMS representative will have access to individual participant data. However, the findings of the interim analysis will be shared with the entire GSK study team.

To:

The interim analysis will be performed by GSK Clinical Statistics and only the responsible statistician (and Quality **control** [QC] statistician) and the CPMS representative will have access to individual participant data. However, the findings of the interim analysis will be shared with the entire GSK study team.

Rationale: to correct a typographical error.

Change 12: Appendix 6, Contraception guidance for female participants

Change from:

Post-menopausal females, under 60 years of age, who are taking HRT and have not had their menopausal status confirmed, must use one of the follow methods of contraception, from dosing until the final visit.

~~1. A condom, with spermicide.~~

2. Male partner sterilization with documentation of azoospermia prior to the female participant's entry into the study, and this male is the sole partner for that participant [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of participant's medical records or medical history interview provided by her or her partner.

~~These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label.~~ The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

To:

Post-menopausal females, under 60 years of age, who are taking HRT and have not had their menopausal status confirmed, must use one of the follow methods of contraception, from dosing until the final visit.

1. Male partner sterilization with documentation of azoospermia prior to the female participant's entry into the study, and this male is the sole partner for that participant [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of participant's medical records or medical history interview provided by her or her partner.

The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

Rationale: to remove condom with spermicide as it is not considered an acceptable method of contraception.

Change 13: Appendix 7, Asthma Control Test

Change from:

Name: _____ Today's Date: _____

ASTHMA CONTROL TEST™

Know your score

The Asthma Control Test™ provides a numerical score to help you and your healthcare provider determine if your asthma symptoms are well controlled.

Take this test if you are 12 years or older. Share the score with your healthcare provider.

Step 1: Write the number of each answer in the score box provided.

Step 2: Add up each score box for the total.

Step 3: Take the completed test to your healthcare provider to talk about your score.

If your score is 19 or less, your asthma symptoms may not be as well controlled as they could be. No matter what the score, bring this test to your healthcare provider to talk about the results.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

If your score is 19 or less, your asthma symptoms may not be as well controlled as they could be. No matter what your score is, share the results with your healthcare provider.

TOTAL: .....

This material was developed by GSK.

To:

Country-specific, commercially available versions of the ACT will be used.

Rationale: to correct the version of the ACT to be used in the study.

12.10.4. Protocol Amendment 4 – Protocol changes for Amendment 04 (02-FEB-2018), from amendment 03 (04-Sep-2017)

Protocol Amendment 4 applies to all sites

Change 1: Section 7.1, Time and Events Table, PEF rows and footnote 18

Change from:

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Out-patient Visits [4,5]											
				Day 1				Day 2	Day 3	Day 4	Week											
			Day –1	Pre-dose	0	2 h	8 h	24 h	48 h	72 h	NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
											Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
PEF [18]			~~X [18]~~																			

~~18.~~ PEF will be recorded ~~**twice** each day **(once in the morning upon waking and once in the evening before bedtime)** during the study from Day −1 onwards. On Days −1 to 3, results will be recorded by the site; on all other days, results will be recorded by the participant, along with any rescue medication use, on diary cards provided by the site.~~ Site staff will review the diary cards at each outpatient visit.

Change to:

Procedure	Pre-Screen [1]	Screen [2]	In-patient Period [3,4]								Out-patient Visits [4,5]											
				Day 1				Day 2	Day 3	Day 4	Week											
			Day –1	Pre-dose	0	2 h	8 h	24 h	48 h	72 h	NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
											Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
PEF Training [18]		**X [18]**																				
PEF [18]		**X [18]**																				

18. PEF will be recorded in the evening before bedtime on the day of the screening visit, then **twice** each day **(once in the morning upon waking and once in the evening before bedtime)** from the day after screening until the end of the study. Training of the participant in how to take measurements will occur at screening. PEF measurements will be taken and results will be recorded by the site while the participant is in-patient at the clinical site (ie from the evening of Day –1 until

the morning of discharge). At all other time points, the participant will record their PEF as instructed, on their diary card, along with any rescue medication use and adverse events. Site staff will review the diary cards at each out-patient Visit.

Rationale: To acquire a better baseline, additional PEF measurements will be recorded from the evening of screening onwards.

Change 2: Section 5.4.3.2, ECG collection timeframe to align with Section 7.3.5

Change from:

Notes: the QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (~~e.g., 5–10 minute~~) recording period.

Change to:

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

Rationale: To align Section 5.4.3.2 and Section 7.3.5 of the protocol to allow QTc values to be obtained from electrocardiograms in a 10 minute time period.

Change 3: Section 6.2, Timeframe for review of available safety data to align with Section 4.1

Change from:

In each cohort, dosing will be staggered: one participant will receive GSK3511294 and one participant will receive placebo at least 72 hours before the remaining participants in that cohort are dosed. ~~If the review of all safety data up to 72 hours after dosing of the first two participants in each cohort is satisfactory,~~ the remaining participants will be dosed. Sentinel dosing is not required in cohorts investigating a dose lower than or equal to the highest dose tested to date.

Change to:

In each cohort, dosing will be staggered: one participant will receive GSK3511294 and one participant will receive placebo at least 72 hours before the remaining participants in that cohort are dosed. Providing no safety issues are identified in the sentinel participants

over an observation period of at least 72 hours, the remaining participants in the cohort may be dosed. Sentinel dosing is not required in cohorts investigating a dose lower than or equal to the highest dose tested to date.

Rationale: To align Section 4.1 and Section 6.2 of the protocol, regarding the observation of sentinel participants in each cohort, prior to dosing the remaining participants in the cohort.

Change 4: Section 4.7.1, Risk Assessment, Risk Mitigation strategy

Change from:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3511294]		
▪ Systemic reactions including allergic reactions.	▪ Systemic reactions including allergic reactions, with the most severe form being anaphylaxis (see Appendix 9), are potential risks associated with mAbs. ▪ Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm or hypotension) have occurred following mepolizumab administration in asthma patients.	▪ Sentinel participants will be used at all dose levels and monitored for at least 72 hours post dose before dosing the remainder of the cohort. ▪ All participants in the UK will have a minimum 72 hour post dose in-patient monitoring period at experienced phase 1 study sites to ensure any late reactions are captured. In Germany this post dose in-patient monitoring period will be 8 days (Appendix 8). ▪ Participants with a history of an allergic sensitivity to biologic agents are excluded. ▪ Any observed reactions will also be treated based on investigator medical judgement (with medical monitor consult as needed). ▪ Investigators will be asked to assess events they consider to represent systemic reactions and events of anaphylaxis against

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Sampson diagnostic criteria for anaphylaxis (Appendix 9).
▪ QTc prolongation	▪ Four monkeys in the 6-month repeat dose monkey study administered 100 mg/kg/week were observed to have QTc prolongation (mean change of 18 msec relative to vehicle control value) during Week 14. ▪ relative to control) at week 14 in the 100 mg/kg dose group only.	▪ ECGs will be performed on a regular basis and should there be any QTc abnormality patients will be monitored more frequently and management instituted as deemed relevant by the Investigator in liaison with the medical monitor. ▪ Participants with QTc prolongation on screening will be excluded. ▪ Participants with a history of cardiac disease, severe hypertension, QTc abnormality or arrhythmia will be excluded as will participants with a relevant family history.

Change to:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3511294]		
▪ Systemic reactions including allergic reactions.	▪ Systemic reactions including allergic reactions, with the most severe form being anaphylaxis (see Appendix 9), are potential risks associated with mAbs. ▪ Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm or hypotension) have	▪ Sentinel participants will be used at all escalating dose levels and monitored for at least 72 hours post dose before dosing the remainder of the cohort. ▪ All participants will have a minimum 72 hour in patient monitoring period at experienced phase 1 study sites to ensure any late reactions are captured.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	occurred following mepolizumab administration in asthma patients.	▪ Participants with a history of an allergic sensitivity to biologic agents are excluded. ▪ Any observed reactions will also be treated based on investigator medical judgement (with medical monitor consult as needed). ▪ Investigators will be asked to assess events they consider to represent systemic reactions and events of anaphylaxis against Sampson diagnostic criteria for anaphylaxis (Appendix 9).
▪ QTc prolongation	▪ Four monkeys in the 6-month repeat dose monkey study administered 100 mg/kg/week were observed to have QTc prolongation (mean change of 18 msec relative to vehicle control value) during Week 14. ▪ relative to control) at week 14 in the 100 mg/kg dose group only.	▪ ECGs will be performed on a regular basis and should there be any QTc abnormality patients will be monitored more frequently and management instituted as deemed relevant by the Investigator in liaison with the medical monitor. ▪ Participants with QTc prolongation on screening will be excluded. ▪ Participants with a history of cardiac disease, Left Bundle Branch Block, Right Bundle Branch Block, severe hypertension, QTc abnormality or arrhythmia will be excluded as will participants with a relevant family history.

Rationale: To clarify that sentinel participants will be used at escalating dose levels only.

Change 5: Section 7.1, Time and Events Table; Demography and Height, Weight and BMI rows

Change from:

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Out-patient Visits [4,5]											
											Week											
			Day –1	Day 1				Day 2	Day 3	Day 4	NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Demography		X																				
Medical history [10]		X																				
Concomitant medication		←																				→
HIV, Hep B and Hep C screen		X																				
FSH and estradiol [8]		X																				
Pregnancy test [9]		X	X											X	X	X	X	X		X [5]	X [5]	X [5]
Drug, alcohol and cotinine screen		X	X																			
Asthma reversibility test	X [11]																					
Genetic sample					X [12]																	
Administer IP					X																	
ACT [13]		X													X		X			X [5]	X [5]	X [5]
Height, weight and BMI		X [14]	X [14]																	X [5,14]	X [5,14]	X [5,14]

14. Height at screening only.

Change to:

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Out-patient Visits [4,5]											
			Day –1	Day 1				Day 2	Day 3	Day 4	Week											
											NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Demography	X																					
Medical history [10]		X																				
Concomitant medication		◄———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———►
HIV, Hep B and Hep C screen		X																				
FSH and estradiol [8]		X																				
Pregnancy test [9]		X	X											X	X	X	X	X		X [5]	X [5]	X [5]
Drug, alcohol and cotinine screen		X	X																			
Asthma reversibility test	X [11]																					
Genetic sample					X [12]																	
Administer IP					X																	
ACT [13]		X													X		X			X [5]	X [5]	X [5]
Height, weight and BMI	X [14]		X [14]																	X [5,14]	X [5,14]	X [5,14]

14. Height at pre-screening or screening only.

Rationale: To clarify that Demography, Height, Weight and BMI will be collected at the pre-screening visit if this visit is required.

Change 6: Section 5.1, Inclusion criterion #3 and #4

Change from:

3. **Asthma**: A physician diagnosis of asthma (mild or moderate, as defined by the Global Initiative for Asthma (GINA), 2017) at least 12 months prior to the start of the study. The reason for diagnosis of asthma should be documented in the participant's source data, including relevant history and investigations – specifically evidence of airway hyperresponsiveness, airflow variation (peak flow rate or FEV_1) or reversible airflow obstruction.

4. ~~Historical evidence of **airway hyperresponsiveness, airflow variation** (peak flow rate or FEV_1) or **reversible airflow obstruction** should be recorded in the participant's source data. If historical evidence of airway hyperresponsiveness, airflow variation (peak flow rate or FEV_1) or reversible airflow obstruction is not available the patient may be included if there is evidence of reversibility on pre-screening or screening.~~

   NOTE:
   - *Airway hyper-responsiveness is defined by a methacholine or histamine concentration of <8 mg/mL producing a ≥ 20% fall in FEV_1.*
   - *Airflow variation is defined as a variation in peak flow rate (the difference between the highest and lowest peak expiratory flow rate expressed as a percentage of the average peak expiratory flow rate) of > 20% over a series of measurements or a variation in FEV_1 > 15% when measured on separate occasions.*
   - *Reversible airway obstruction is defined as increase in FEV_1 of ≥ 12% over baseline AND an absolute change of ≥ 200 mL ~~within 30 minutes~~ following 4 inhalations of albuterol/salbutamol inhalation aerosol/spacer (or equivalent nebulised treatment with albuterol/salbutamol solution).*

Change to:

3. **Asthma**: A physician diagnosis of asthma (mild or moderate, as defined by the Global Initiative for Asthma (GINA), 2017) at least 12 months prior to the start of the study. The reason for diagnosis of asthma should be documented in the participant's source data, including relevant history. If available, investigations – specifically evidence of airway hyperresponsiveness, airflow variation (peak flow rate or FEV_1) or reversible airflow obstruction, should also be documented in the participant's source data.

   - *NOTE: Airway hyper-responsiveness is defined by a methacholine or histamine concentration of <8 mg/mL producing a ≥ 20% fall in FEV_1.*
   - *Airflow variation is defined as a variation in peak flow rate (the difference between the highest and lowest peak expiratory flow rate expressed as a percentage of the average peak expiratory flow rate) of > 20% over a series of measurements or a variation in FEV_1 > 15% when measured on separate occasions.*
   - *Reversible airway obstruction is defined as increase in FEV_1 of ≥ 12% over baseline AND an absolute change of ≥ 200 mL following 4 inhalations of*

albuterol/salbutamol inhalation aerosol/spacer (or equivalent nebulised treatment with albuterol/salbutamol solution).

Rationale: To remove the necessity for evidence of airway hyperresponsiveness, airflow variation (peak flow rate or FEV_1) or reversible airflow obstruction.

Change 7: Section 5.3, Screening/Baseline/Run-in Failures

Change from:

Screening/Baseline/Run-in Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently randomised. In order to ensure transparent reporting of screen failure participants, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.5).

Change to:

Pre-screening/Screening/Baseline/Run-in Failures

Pre-screening failures are defined as participants who consent to participate in a clinical trial, attend the Pre-screening visit but do not meet the criteria for the screening visit (blood eosinophils ≥200 cells/μL). Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently randomised. In order to ensure transparent reporting of screen failure participants, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.3.1.5).

Rationale: To clarify the definition of a pre-screening failure.

Change 8: Section 6.10.2, Added live vaccines to the prohibited concomitant medication list

Change from:

The following asthma medications are prohibited during the study and within the timeframe indicated in brackets before screening:

- Immunotherapy (at any time)
- Desensitization therapy (ongoing)
- anti-IgE therapy (within 6 months)
- anti-IL5 (within 6 months)
- oral or injectable corticosteroids (within 8 weeks)
- LAMA or LTRA therapy (within 8 weeks)

Change to:

The following asthma medications are prohibited during the study and within the timeframe indicated in brackets before screening:

- Immunotherapy (at any time)
- Desensitization therapy (ongoing)
- anti-IgE therapy (within 6 months)
- anti-IL5 (within 6 months)
- oral or injectable corticosteroids (within 8 weeks)
- LAMA or LTRA therapy (within 8 weeks)
- Live vaccines

Rationale: To clarify that no patient is allowed to receive a live vaccine at any point during study participation.

Change 9: Section 5.2, addition of Right Bundle Branch Block as an exclusion criteria. Section 5.4.3.2, QTc

Change from:

Section 5.2:

12. **QTc** > 450 msec ~~or QTc > 480 msec in participants with Right Bundle Branch Block.~~
    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 or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).*
13. A personal history of **severe hypertension, arrhythmia or Left Bundle Branch Block**, or a family history of **sudden unexplained death, long QT, familial cardiac syndrome, or cardiomyopathy**.

Section 5.4.3.2:

<u>Direct observation for 24 hours</u> before discharge with 48 hour ambulatory Holter monitor and subsequent repeat assessment at 48 hours *****.

- QT or QTc change from baseline ≥ 60 msec and no clinical impact. (Baseline is the average of triplicate readings at pre-dose on Day 1.)
- QTc > 500 msec or uncorrected QT > 600 msec and no clinical impact.

***** To remain under observation if QT/QTc remains the same/increases on assessment at 24 (end of direct observation) and 72 hours periods (after 48 hour Holter monitor) and for consideration of cardiology consult.

~~For participants with underlying **bundle-branch block**, follow the evaluation criteria listed below:~~

- ~~Baseline QTc < 450 msec, increase monitoring at QTc > 500 msec~~
- ~~Baseline QTc between 450 to 480 msec, increase monitoring at QTc ≥ 530 msec~~

Change to:

Section 5.2

12. **QTc** > 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 or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).*
13. A personal history of **severe hypertension, arrhythmia, Right Bundle Branch Block, or Left Bundle Branch Block**, or a family history of **sudden unexplained death, long QT, familial cardiac syndrome, or cardiomyopathy**.

Section 5.4.3.2:

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

- QT or QTc change from baseline ≥ 60 msec and no clinical impact. (Baseline is the average of triplicate readings at pre-dose on Day 1.)
- QTc > 500 msec or uncorrected QT > 600 msec and no clinical impact.

***** To remain under observation if QT/QTc remains the same/increases on assessment at 24 (end of direct observation) and 72 hours periods (after 48 hour Holter monitor) and for consideration of cardiology consult.

Rationale: To safely exclude all participants with Right Bundle Branch Block

Change 10: Section 5.5, Study halting criteria

Change from:

The study may continue, if, after review, the sponsor and investigators consider it safe to do so. However, the study may re-start only after ethics and regulatory approval of a substantial amendment.

Change to:

Participants who have been dosed at the time of the study halt will continue in the study, as planned. Further participants may be dosed only if, after review, the sponsor and investigators consider it safe to do so and only after ethics and regulatory approval of a substantial amendment.

Rationale: To clarify the study halting criteria

Change 11: Section 10.2, Regulatory and Ethical Considerations, Including the Informed Consent Process

Change from:

- Signed informed consent must be obtained for each participant prior to participation in the study

Change to:

- Signed informed consent must be obtained and available for each participant prior to participation in the study

Rationale: To clarify the informed consent process and that informed consent must be available prior to inclusion in the study

Change 12: Section 5.2, Exclusion Criteria, Other

Addition of participants who are institutionalised on regulatory or court order as an exclusion criteria

33. Vulnerable subjects, e.g., participants kept in detention, protected adults under guardianship, trusteeship and soldiers, or participants committed to an institution by governmental or juridical order.

Rationale: To ensure exclusion of such participants from the study as this may hinder their ability to comply with study procedures/requirements.

Change 13: Section 12.8.1, Country Specific Requirements

Addition of:

13.8.2 Additional Hepatitis B Core Antibody test for inclusion of participants in Germany

In order to comply with German requirements for Hepatitis B virus testing in Germany, participants will be tested for the hepatitis B core antibody (anti-HBc) at screening. The German-specific exclusion criterion 5 is as follows:

Positive for **hepatitis B** surface antigen (HBsAg) and core antibody (anti-HBc) at screening.

Table 5 has been updated accordingly.

Table 5 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices*:	WBC count with Differential:	
	RBC Count	MCV	*(post-dose results blinded as described in footnote 1)*	
			WBC	
	Hemoglobin	MCH	Neutrophils	
	Haematocrit		Lymphocytes	
			Monocytes	
			Eosinophils	
Clinical Chemistry	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose (fasted at screening)	Calcium	Alkaline phosphatase	Albumin
		Magnesium		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination and UACR (if blood or protein is abnormal [evidence of microbalbinumaemia or haematuria of ≥ 1+])			
Other tests	• hsCRP			
Other Screening Tests	• HIV • Hepatitis B (HBsAg; in Germany only, anti-HBc will also be tested [Appendix 8]) • Hepatitis C (Hep C antibody) • FSH and estradiol (if required to confirm postmenopausal status) • Alcohol, cotinine and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)			

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BUN = blood urea nitrogen; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; anti-HBc = hepatitis B core antibody; hsCRP = highly sensitive C-reactive protein; MCH = mean corpuscular haemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; UACR = urinary albumin-creatinine ratio; WBC = white blood cell, pH= hydrogen ion concentration.

1. The following post-dose results will be blinded to Investigators and blinded Sponsor representatives: total WBCs; absolute and percentage eosinophils; and percentage neutrophils, lymphocytes, monocytes and basophils.

12.8.2 Additional In-patient stay period for participants from Germany

In Germany, participants will remain in-patient for a minimum of 8 days post dosing, as noted in Section 4.2, Section 4.7.1 and Section 7.1. For clarity, the time and events table for Germany is provided below:

Section 4.2, Treatment Arms and Duration

- In-patient period: Participants will be admitted the day before dosing, and the minimum post dose in-patient period for all participants will be 72 hours in the UK and 8 days in Germany (Appendix 8). Participants will be monitored for local injection site reactions and allergic reactions for at least 72 hours post dose. In the case of such reactions, appropriate medical treatment will be administered. Participants will be discharged only if the Investigator deems it safe for the participant to leave the unit (For further information regarding the in-patient period in Germany, please refer to Section 12.8.2).
- Total duration: The scheduled maximum study duration for each participant who receives GSK3511294 or placebo will be up to 44 weeks (excluding pre-screening for blood eosinophils), including up to 28 days for screening, 4 days as an in-patient in the UK and 9 days in Germany (Appendix 8), and up to 40 weeks post-dosing to investigate the PD (blood eosinophil count) and safety profile.

Rationale: To accommodate the requirements of the Regulators and Ethics Committee from Germany.

4.7.1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3511294]		
Duration of in-patient stay after dosing	Tmax of GSK3511294 is expected at 7−10 days after dosing. However, any significant side effect of GSK3511294 in the time to Tmax is most likely to be an anaphylactic reaction, which would occur in the first 72 hours after dosing. The predicted PK profile indicates approximately 80% of Cmax at 72 hours after dosing. Participants will have a minimum 72 hour in patient monitoring period at experienced phase 1 study. Therefore, to minimise the inconvenience to participants, they may be discharged from the clinical unit 72 hours (or longer) after dosing, provided that the Investigator considers them well enough to leave.	▪ In the UK, Investigators will review available safety data up to 72 hours to confirm participants are well enough to leave the clinical unit. In Germany, in response to regulatory comments, participants will be in-patient until at least 8 days after dosing. ▪ Participants will receive a medical alert card, with details of the study, clinical site and Investigator, when they are discharged from the unit. They will be instructed to contact the unit with any safety concerns they might have, and to show the medical alert card to any other medical professional they might consult.

7.1 Time and Events Table

Procedure	Pre-Screen [1]	Screen [2]	In-patient Period [3,4]								Out-patient Visits [4,5]													
											Week													
			Day –1	Day 1				Day 2	Day 3	Day 4	NA	1	NA	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day													
											5	8	9	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Informed consent	X [6]																							
Pre-screening Blood eosinophils	X [7]																							
Inclusion & exclusion criteria		X	X	X																				
Demography	X																							
Medical history [10]		X																						
Concomitant medication		◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
HIV, Hep B and Hep C screen		X																						
FSH and estradiol [8]		X																						
Pregnancy test [9]		X	X												X	X	X	X	X		X [5]	X [5]	X [5]
Drug, alcohol and cotinine screen		X	X																					
Asthma reversibility test	X [11]																							
Genetic sample					X [12]																			
Administer IP					X																			
ACT [13]		X														X		X			X [5]	X [5]	X [5]
Height, weight and BMI	X [14]		X [14]																		X [5,14]	X [5,14]	X [5,14]
Full phys exam		X																			X [5]	X [5]	X [5]
Brief phys exam			X			X				X		X				X								

Procedure	Pre-Screen [1]	Screen [2]	In-patient Period [3,4]								Out-patient Visits [4,5]												
											Week												
											NA	1	NA	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
			Day –1	Day 1				Day 2	Day 3	Day 4	Day												
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	5	8	9	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Dispense rescue SABA		X	Resupply, as required.																				
Haematology (including blood eosinophil count), Clin. Chem., Urinalysis and hsCRP		X	X					X	X	X	X	X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Serum save (for immunological analysis, if needed)		X				Ad hoc, as required by symptoms – see Appendix 3.																	
Inflammatory markers		X				Ad hoc, as required by symptoms – see Appendix 3.																	
Complement (C3 & C4)		X	X					X	X	X	X			X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Total IgE			X					X	X	X	X				X	X	X	X	X		X [5]	X [5]	X [5]
PK Blood Samples				See Table 4.																			
Immunogenicity				X										X	X	X	X	X	X	X	X [5]	X [5]	X [5]
CICs				X				X						X	X	X	X	X	X	X	X [5]	X [5]	X [5]
12-lead ECG [15]		X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Vital signs [16]		X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]
AE/SAE review (inc local ISR up to 72 h after dosing)	X [17]		◄																				►
IL-5 sample			X					X	X			X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]

Procedure	Pre-Screen [1]	Screen [2]	In-patient Period [3,4]								Out-patient Visits [4,5]													
											Week													
			Day –1	Day 1				Day 2	Day 3	Day 4	NA	1	NA	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day													
											5	8	9	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Exploratory biomarkers of asthma in blood			X												X			X					
Spirometry		X	X			X		X		X		X				X					X [5]	X [5]	X [5]
PEF Training [18]		X																					
PEF [18]		X [18]																					
Diary review [18]											X	X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]

Abbreviations: ACT = Asthma Control Test; AE = adverse event; BMI = body mass index; CICs = circulating immune complexes; CRP = C-reactive protein; ECG = electrocardiogram; FSH = follicle stimulating hormone; h = hour(s); Hep B = Hepatitis B; Hep C = Hepatitis C; HIV = human immunodeficiency virus; IgE = immunoglobulin E; IL-5 = interleukin-5; IP = Investigational Product; ISR = injection site reactions; PEF = peak expiratory flow; PK = pharmacokinetic; SABA = short acting β-agonist; SAE = serious adverse event.

Notes:

1. Pre-screen up to 12 weeks before dosing. Blood eosinophils must be ≥ 200 cells/μL for participants to proceed to screening. Blood eosinophil count may be existing data or obtained at a pre-screen visit.
2. Screening up to 4 weeks before randomisation. Screening procedures may be done at one or more visits, within the screening window.
3. In the UK, all participants will be in-patient for at least 72 h after dosing. In Germany, all participants will be in-patient for at least 8 days after dosing (see Appendix 8 for the German-specific time and events table).
4. Allowed time deviations will be documented in the Study Reference Manual.
5. All participants will have all out-patient visits up to Week 26 after dosing. Each cohort will also have out-patient visits after week 26, depending on the dose, as follows:
   - 2 and 10 mg: Week 32 only
   - 30 mg and 100 mg: Week 36 only
   - 300 mg: Weeks 32 and 40

   (For unplanned dose levels, the timing of out-patient visits will be documented in a Note to File.)
6. Informed consent will be taken either at the pre-screen visit, for participants who don't have an existing eosinophil count, or at screening, for those who do.
7. Blood eosinophils will be included in the haematology panel at all time points other than the pre-screen visit.
8. If required to confirm postmenopausal status.
9. Women on hormone replacement therapy, whose post-menopausal status cannot be confirmed, only.
10. Including cardiovascular (CV) disease, asthma exacerbation, and drug, alcohol and smoking history.
11. At pre-screening or screening, only if historical data (as described in inclusion criterion 4) is unavailable.

12. If the participant consents, an optional, genetic sample will be collected once during the study.
13. At each applicable visit, ACT should be done before any other assessment.
14. Height at pre-screening or screening only.
15. ECGs triplicate at all time points. ECGs should be time-matched to baseline (i.e. pre-dose on Day 1) from Day 2 onwards.
16. Blood pressure and heart rate in triplicate before dosing; single measurements after dosing. Single temperature and respiratory rate measurements at all time points.
17. Only SAEs are collected before dosing (see Section 7.3.1).
18. PEF will be recorded in the evening before bedtime on the day of the screening visit, then **twice** each day **(once in the morning upon waking and once in the evening before bedtime)** from the day after screening until the end of the study. Training of the participant in how to take measurements will occur at screening. PEF measurements will be taken and results will be recorded by the site while the participant is in-patient at the clinical site (ie from the evening of Day –1 until the morning of discharge). At all other time points, the participant will record their PEF as instructed, on their diary card, along with any rescue medication use and adverse events. Site staff will review the diary cards at each out-patient Visit.

Change 14: Section 7.4.1, Blood sample collection and Appendix 2 (footnote 4), Liver Safety Requirements; reference to appropriate lab manual for instructions regarding PK samples

Change from:

Section 7.4.1, Blood sample collection

Processing, storage and shipping procedures are provided in the SRM.

Appendix 2, Liver Safety Requirements (footnote 4)

PK sample may not be required for participants known to be receiving placebo. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If 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.

Change to:

Section 7.4.1, Blood sample collection

Processing, storage and shipping procedures are provided in the appropriate lab manual.

Appendix 2, Liver Safety Requirements (footnote 4)

4) PK sample may not be required for participants known to be receiving placebo. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If 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 appropriate lab manual.

Rationale: To clarify that information regarding the handling of PK samples will be located in the appropriate lab manual and not the SRM.

Change 15: Section 7.3.6, Clinical Safety Laboratory Assessments, addition of footnote 1

Change from:

Laboratory Assessments	**Parameters**		
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*
	RBC Count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Haematocrit		Monocytes
			Eosinophils (post-dose results to be blinded to investigators)
			Basophils

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BUN = blood urea nitrogen; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; hsCRP = highly sensitive C-reactive protein; MCH = mean corpuscular haemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; UACR = urinary albumin-creatinine ratio; WBC = white blood cell, pH= hydrogen ion concentration.

Change to:

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td>Haematology</td><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>WBC count with Differential</u> (post-dose results blinded as described in footnote 1):</td></tr>
<tr><td rowspan="2">RBC Count</td><td rowspan="2">MCV</td><td>WBC</td></tr>
<tr><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Haematocrit</td><td rowspan="3"></td><td>Monocytes</td></tr>
<tr><td rowspan="2"></td><td>Eosinophils</td></tr>
<tr><td>Basophils</td></tr>
</table>

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BUN = blood urea nitrogen; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; anti-HBc = hepatitis B core antibody; hsCRP = highly sensitive C-reactive protein; MCH = mean corpuscular haemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; UACR = urinary albumin-creatinine ratio; WBC = white blood cell, pH= hydrogen ion concentration.

1. The following post-dose results will be blinded to Investigators and blinded Sponsor representatives: total WBCs; absolute and percentage eosinophils; and percentage neutrophils, lymphocytes, monocytes and basophils.

Rationale: To ensure there is no un-blinding that can occur for Eosinophil counts due to availability of other components and their contributions to WBC count.

12.10.5. Protocol Amendment 5 – Protocol changes for Amendment 05 (18-Jun-2018), from amendment 04 (02-Feb-2018)

Change 1: Section 4.3, Dose Escalation; Section 5.4.3.2, Criteria for increased monitoring of individual participants, QTc

Change from:

Section 4.3, Dose Escalation

- The dose will not be escalated, nor will a dose level be repeated, if, at that dose level:
  - one or more of the study halting criteria are met (see Section 5.5)
  - one or more participants has experienced at least one of the criteria for potential type III hypersensitivity/immune complex disease, and there is ongoing clinical concern about the participant's condition (see Section 5.4.2)
  - one or more participants has a QTc > 500 msec or uncorrected QT > 600 msec, or an increase in QT/QTc ≥ 60 msec

Section 5.2, Exclusion Criteria

12. **QTc** > 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 or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).*

Section 5.4.3.2, Criteria for increased monitoring, QTc

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

- QT or QTc change from baseline ≥ 60 msec and no clinical impact. (Baseline is the average of triplicate readings at pre-dose on Day 1.)
- QTc > 500 msec or uncorrected QT > 600 msec and no clinical impact.

* To remain under observation if QT/QTc remains the same/increases on assessment at 24 (end of direct observation) and 72 hours periods (after 48 hour Holter monitor) and for consideration of cardiology consult.

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

Section 7.3.5, Electrocardiogram (ECG)

- 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section

5.4.3.2 for QTc increased monitoring criteria and additional QTc readings that may be necessary.

The 12-lead ECG will be performed in the supine position. At all time points, after a 5 minutes rest, triplicate ECGs will be obtained over a brief recording period (up to 10 minutes). The ECGs will be time-matched to baseline assessment (ie pre-dose on Day 1) from Day 2 onwards.

Change to:

Section 4.3, Dose Escalation

- The dose will not be escalated, nor will a dose level be repeated, if, at that dose level:
  - one or more of the study halting criteria are met (see Section 5.5)
  - one or more participants has experienced at least one of the criteria for potential type III hypersensitivity/immune complex disease, and there is ongoing clinical concern about the participant's condition (see Section 5.4.2)
  - one or more participants has a QTcF > 500 msec or uncorrected QT > 600 msec, or an increase in QTcF > 60 msec, in the absence of any other identifiable reason (e.g. concomitant medication). In such a scenario, if after review of all clinical safety data for the participant(s), the increased QT is considered to be isolated and not clinically significant in the opinion of the medical monitor and investigators, dose escalation and/or dosing of further patients at the dose level at which the event was observed can occur only after ethics and regulatory approval of a substantial amendment.

Section 5.2, Exclusion Criteria

12. **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 or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).*

Section 5.4.3.2 Criteria for increased monitoring, QTc

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

- 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.

* To remain under observation if QTcF (or QT if > 600 msec) remains the same/increases on assessment at 24 (end of direct observation) and 72 hours periods (after 48 hour Holter monitor) and for 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.

Section 7.3.5, Electrocardiogram (ECG)

- 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.3.2 for QTc increased monitoring criteria and additional QTc readings that may be necessary.

The 12-lead ECG will be performed in the supine position. At all time points, after a 5 minutes rest, triplicate ECGs will be obtained over a brief recording period (up to 10 minutes). The ECGs will be time-matched to baseline assessment (ie pre-dose on Day 1) from Day 2 onwards. For QT interval corrected for heart rate (QTc), for the purposes of standardisation, Fridericia's correction formula (QTcF) was selected and will be used across sites with central over-read to limit variability.

Rationale: A raw QT interval change from baseline as one of the criteria for limiting dose escalation and for increased monitoring of individual participants has been included in error. QTcF has been chosen as the most appropriate corrective measure of QT for this study and this is now reflected throughout. Accordingly, one of the required criteria for limiting further dose escalation and increased monitoring of individuals is now a change in QTcF from baseline of > 60 msec.

Change 2: Section 5.3, Pre-screening/Screening/Baseline/Run-in Failures

Addition of:

Participants who would not have been a screen failure on the basis of the entry criteria in the current version of the protocol may be rescreened for entry into the study. Participants who could not be dosed for logistical reasons within the permissible screening window after passing screening for a cohort, may be rescreened for entry into a subsequent cohort. Rescreened participants should be assigned a new participant number.

Rationale: To allow rescreening of a participant if they were not a screen failure, or would not have been one under the current version of the protocol.

Change 3: Section 6.10.1, Permitted Medications and Non-Drug Therapies; Section 7.1, Time and Events Table, Section 7.2, Screening and Critical Baseline assessments; Section 12.8, Appendix 8, Country Specific Requirements

Change from:

Section 6.10.1, Permitted Medications and Non-Drug Therapies

Asthma medication will be temporarily withheld before the reversibility test at pre-screening or screening, and spirometry assessments at screening and on Day –1: SABAs will be withheld for 6 hours; LABAs will be withheld for 12 hours; and LABAs with ultra-long activity will be withheld for 24 hours.

7.1, Time and Events Table

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Out-patient Visits [4,5]											
			Day –1	Day 1				Day 2	Day 3	Day 4	Week											
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
											Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Drug, alcohol and cotinine screen		X	X																			
Asthma reversibility test	X [11]																					
Genetic sample					X [12]																	

11. At pre-screening or screening, only if historical data (as described in inclusion criterion 4) is unavailable.

Section 7.2, Screening and Critical Baseline assessments

The Asthma Control Test (Appendix 7) should be completed by participants before any other assessment at a clinic visit, in the order specified.

A reversibility test will be done at screening, as described in the SRM. See Section 6.10.1 for medication restrictions before the test.

Section 12.8.2, Appendix 8, Country Specific Requirements

Procedure	Pre-Screen [1]	Screen [2]	In-patient Period [3,4]								Out-patient Visits [4,5]												
			Day –1	Day 1				Day 2	Day 3	Day 4	Week												
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	NA	1	NA	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
											Day												
											5	8	9	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Drug, alcohol and cotinine screen		X	X																				
Asthma reversibility test	X [11]																						
Genetic sample					X [12]																		

11. At pre-screening or screening, only if historical data (as described in inclusion criterion 4) is unavailable.

Change to:

Section 6.10.1, Permitted Medications and Non-Drug Therapies

Asthma medication will be temporarily withheld before spirometry assessments at screening and on Day –1: SABAs will be withheld for 6 hours; LABAs will be withheld for 12 hours; and LABAs with ultra-long activity will be withheld for 24 hours.

7.1, Time and Events Table

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Out-patient Visits [4,5]											
			Day –1	Day 1				Day 2	Day 3	Day 4	Week											
											NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Drug, alcohol and cotinine screen		X	X																			
Genetic sample					X [11]																	

Section 7.2, Screening and Critical Baseline assessments

The Asthma Control Test (Appendix 7) should be completed by participants before any other assessment at a clinic visit, in the order specified.

Section 12.8, Appendix 8, Country Specific Requirements

Procedure	Pre-Screen [1]	Screen [2]	In-patient Period [3,4]								Out-patient Visits [4,5]											
			Day –1	Day 1				Day 2	Day 3	Day 4	Week											
											NA	1	NA	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day											
											5	8	9	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Drug, alcohol and cotinine screen		X	X																			
Genetic sample					X [11]																	

Rationale: To clarify that, because reversibility is no longer an inclusion criterion in the most recent version of the protocol, there is no need for it to be performed at pre-screening or screening.

Change 4: Section 7.1, Time and Events table, Table 4

Change from:

Table 4 Pharmacokinetic sampling time points

Dose level	Pre-dose	Post-dose															
		Hours				Days											
		2	8	24	48	5	8	15	29	57	85	127	169	183	225	253	281
2 mg and 10 mg	X	X	X	X	X	X	X	X	X	X	X						
30 mg and 100 mg	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
300 mg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Notes: For unplanned dose levels, PK sampling time points will be documented in a Note to File.

Pharmacokinetic sampling time points

Dose level	Pre-dose	Post-dose															
		Hours				Days											
		2	8	24	48	5	8	15	29	57	85	127	169	183	225	253	281
2 mg and 10 mg	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
30 mg and 100 mg	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
300 mg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Notes: For unplanned dose levels, PK sampling time points will be documented in a Note to File.

Rationale: Extension of the PK sampling period is required for participants in cohorts 1 and 2, in order to better characterise the PK profile of GSK3511294.

Change 5: Section 7.3.6, Clinical Safety Laboratory Assessments

Change from:

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed – for example: on Day –1, when results should be available before dosing on Day 1; at 48 h post-dose, when results should be available before the participant is discharged from the clinical unit; or at any other time when a participant is unwell and results are required urgently. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Change to:

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed – for example: on Day –1, when results should be available before dosing on Day 1; at 48 h post-dose for all sentinel participants; at 48 h post-dose when results should be available before the participant is discharged from the clinical unit in the UK; on Day 8, when results should be available before the participant is discharged from the clinical unit in Germany; or at any other time when a participant is unwell and results are required urgently. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Rationale: To clarify that local labs are required for all sentinel participants at the 48 hour time point to enable dosing of the rest of the cohort. As the German in-patient stay is longer than the UK, local labs prior to discharge from the clinical site are required on Day 8 and not at 48 hours post dosing (Day 3).

12.10.6. Protocol Amendment 6 – Protocol changes for Amendment 06 (07-JAN-2019), from Amendment 05 (18-JUN-2018)

A description of changes and rationale are provided below. The opportunity to make corrections to very minor typographical errors has been taken.

Change 1: Section 1.2., Study Rationale

Change from:

In stream data review will occur during the study to support dose escalation decisions, and a formal interim analysis is planned once the accumulated safety, PK and PD data is deemed sufficient to determine the doses, and dosing interval, to take forward to the next phase of development.

Change to:

In stream data review will occur during the study to support dose escalation decisions, and formal interim analyses are planned to ensure accumulated safety, PK and PD data is deemed sufficient to determine the doses, and dosing interval, to take forward to the next phase of development.

Change 3: Section 6.3., Blinding

Change from:

A formal unblinded interim analysis will be performed by GSK (see Section 9.3.2)

Change from:

Formal unblinded interim analyses will be performed by GSK (see Section 9.3.2)

Change 2: Section 9.3.2., Interim Analyses

Change from:

In stream data review will occur during the study to support dose escalation decisions, with a formal interim analysis planned once the accumulated safety, PK and PD data is deemed sufficient to determine the doses and a dose interval to move forward into the next phase of development, but is not expected to affect the progression of this FTIH study.

Currently, the interim analysis is projected to occur once data is available at the 12-week time point after dosing in Cohort 4 (planned 100 mg dose). The primary focus of the interim analysis will be reduction in blood eosinophil counts. The ratio to baseline will be derived for each dose and time point and will be compared to corresponding data from the placebo arm. Posterior means and corresponding 95% credible intervals will be constructed for each of the available doses and time points. Furthermore, posterior probabilities that the placebo adjusted ratio is less than various thresholds of interest will be constructed.

The interim analysis will be performed by GSK Clinical Statistics and only the responsible statistician (and Quality control [QC] statistician) and the CPMS representative will have access to individual participant data. However, the findings of the interim analysis will be shared with the entire GSK study team.

Change to:

In stream data review will occur during the study to support dose escalation decisions, and formal interim analyses are planned to ensure accumulated safety, PK and PD data is deemed sufficient to determine the doses and dosing interval to move forward into the next phase of development but is not expected to affect the progression of this FTIH study.

Currently, the first interim analysis is projected to occur once data is available at the 12-week time point after dosing in Cohort 4 (planned 100 mg dose). The primary focus of this interim analysis will be reduction in blood eosinophil counts. The ratio to baseline will be derived for each dose and time point and will be compared to corresponding data from the placebo arm. Posterior means and corresponding 95% credible intervals will be constructed for each of the available doses and time points. Furthermore, posterior probabilities that the placebo adjusted ratio is less than various thresholds of interest will be constructed.

The earliest next interim analysis is planned no earlier than once data is available at the 26-week time point after dosing Cohort 4 (planned 100 mg dose). The primary focus of this and potential subsequent interim analyses will be the same as the first interim analysis (described above).

The interim analyses will be performed by GSK Clinical Statistics and only the responsible statistician (and Quality control [QC] statistician) and the CPMS

representative will have access to individual participant data. However, the findings of the interim analyses will be shared with the entire GSK study team.

Rationale: Inclusion of additional interim analyses to better assess blood eosinophil count return towards baseline profiles at the highest dose levels investigated and better inform dose and dosing regimen to move forward into the next phase of development. The earliest additional interim analysis is planned no earlier than once data is available at the 26-week time point after dosing Cohort 4 (planned 100 mg dose).