TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	An open label, randomised, three arm, single dose, multicentre, parallel group study in healthy subjects to compare the pharmacokinetics of subcutaneous mepolizumab when delivered as a liquid drug product in a safety syringe or an auto injector with a reconstituted lyophilised drug product from a vial

Compound Number: SB240563

Development Phase: III

Effective Date: 10-JUL-2017

Protocol Amendment Number: 03

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N275057_00	2016-AUG-31	Original
2016N275057_01	2016-NOV-05	Amendment No. 1
Update to the content of the Device error forms to reflect consistency with other data captured in similar studies. Updated withdrawal wording Section 5.4.1. Removal of Cardiovascular and deaths events Section 7.3.1.4.		
2016N275057_02	2016-NOV-17	Amendment No. 2
Minor changes incorporated throughout the document as part of the QC step.		
2016N275057_03	2017-JUL-10	Amendment No.3
Section 7.3.1.4 Cardiovascular and Death Events section has been removed. Subsequent Section 7.3.1.5 “Regulatory reporting requirements for SAE’s” is assigned Section number 7.3.1.4 to maintain numerical sequence.		

SPONSOR SIGNATORY

PPD

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Physician Project Lead, Medicines Development Center, Global Clinical Development, US Respiratory R&D

July 10, 2017
DATE

PPD

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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.

IND No: 006971, EudraCT No: 2016-002405-19

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number **204958**

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 204958

Rationale

Mepolizumab (SB-240563) is a humanized monoclonal antibody (IgG1, kappa, mAb) that blocks human interleukin-5 (hIL-5) from binding to the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits signaling. Neutralization of IL-5 with mepolizumab reduces blood, sputum and tissue eosinophils, which results in a reduction in exacerbations/flares and in the maintenance dose of oral corticosteroids (OCS) in various eosinophilic-mediated diseases.

Mepolizumab has been investigated for the treatment of patients with severe eosinophilic asthma who have current blood eosinophil levels of 150 cells/μL or greater, or historical blood eosinophil levels (within 12 months) of 300 cells/μL or greater and history of exacerbations despite high dose inhaled corticosteroid therapy and an additional controller. It has been recently approved in a number of markets including the EU (03 December 2015) and US (04 November 2015). Mepolizumab has also been evaluated in subjects with moderate asthma, FIP1L1/PDGFRα-negative hypereosinophilic syndrome (HES), eosinophilic esophagitis (EoE) and eosinophilic granulomatosis with polyangiitis (EGPA) (i.e. Churg Strauss syndrome).

Mepolizumab for Injection, a sterile, single-use, preservative-free, lyophilized drug product formulation (herein referred to as lyophilized drug product) was used in the clinical development programs and is the current marketed presentation for asthma (Nucala™). Before use, each vial of lyophilized drug product must be reconstituted with water for injection (WFI) using aseptic techniques. As part of the life cycle of mepolizumab, a liquid drug product provided as a ready-to-use pre-filled syringe assembled into either a safety syringe or an autoinjector, Mepolizumab Injection, has been developed. Administration of Mepolizumab Injection (herein referred to as liquid drug product in autoinjector or liquid drug product in safety syringe) will be more convenient and may allow the ultimate goal of patient self-administration.

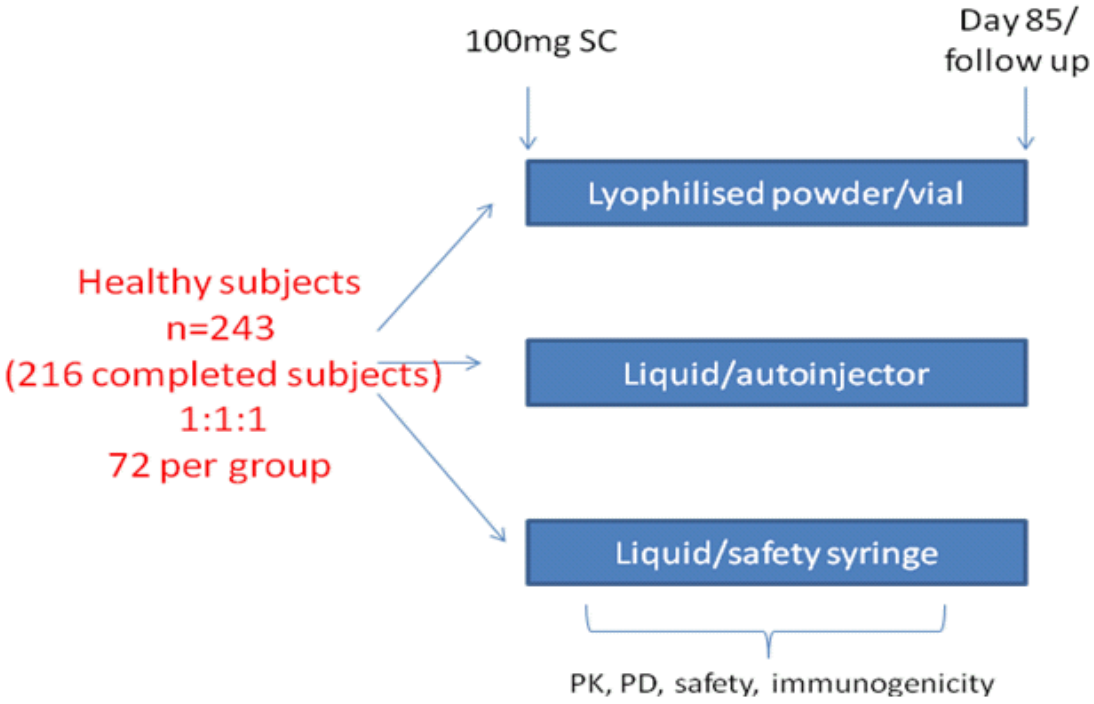
In vitro analytical data confirms that the liquid and lyophilised formulations of mepolizumab are comparable. Consequently the likelihood of clinically significant differences in the systemic exposure, efficacy or safety profile between the liquid drug product in the safety syringe or autoinjector and the lyophilised powder for reconstitution in the vial is considered to be low. However, in addition to demonstration of in vitro biochemical comparability, the change in formulation and the change in drug product presentation from a manually administered reconstituted lyophile to a liquid (administered from a safety syringe or autoinjector) requires demonstration clinically that the relative bioavailability of the treatments are similar (ICHQ5E; biopharmaceutical comparability).

The aim of this study is to provide relative bioavailability data to support the transition from the currently marketed presentation of the lyophilised powder for reconstitution to a ready-to-use liquid in a pre-filled syringe assembled into either a safety syringe or an autoinjector. The study is intended to demonstrate comparable mepolizumab pharmacokinetics following a single subcutaneous (SC) dose administration in healthy subjects. Safety (including immunogenicity) and tolerability will also be evaluated. Blood eosinophil count and device functionality will also be explored.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the pharmacokinetics of subcutaneous mepolizumab following a single dose of the. liquid drug product in safety syringe with the lyophilized drug product	• Mepolizumab PK parameters: Cmax, AUC(0-t) and AUC(0-∞).
• To compare the pharmacokinetics of subcutaneous mepolizumab following a single dose of the liquid drug product in autoinjector with the lyophilized drug product.	• Mepolizumab PK parameters: Cmax, AUC(0-t) and AUC(0-∞).
Secondary	
• To assess additional pharmacokinetic parameters following mepolizumab subcutaneous administration of the liquid drug product in autoinjector or the liquid drug product in safety syringe in comparison with the lyophilized drug product, as data permit	• tmax, CL/F, Vd/F, λz, t ½, tlast, %AUCex.
• To assess the safety and tolerability of mepolizumab following a single SC dose of the liquid drug product in autoinjector or the liquid drug product in safety syringe in comparison with the lyophilised drug product	• Adverse events (AEs), serious adverse events (SAEs), including systemic reactions and injection site reactions. • Haematology and Clinical Chemistry • Vital signs • 12-lead ECG
• To assess the immunogenicity of mepolizumab following a single SC dose of the liquid drug product in autoinjector or the liquid drug product in safety syringe in comparison with the lyophilised drug product	• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies

Overall Design



This will be a randomised, open label, three arm, single dose, multicentre, parallel group study in healthy subjects. Three different mepolizumab treatments will be administered:

- a liquid drug product in a safety syringe (test),
- a liquid drug product in an autoinjector (test),
- a reconstituted lyophilised drug product from a vial (reference).

All treatments will be administered **SC** by a health care professional (HCP). The study will compare the pharmacokinetics and safety of mepolizumab administered as a liquid drug product in two different devices with the reconstituted lyophilised drug product. Blood eosinophil count and device functionality will also be explored. Subjects will receive 100 mg mepolizumab SC as a single injection. The randomisation will be stratified by body weight (<70kg, 70-<80kg and ≥80kg). The site of injection will be randomised 1:1:1 to the upper arm, abdomen or thigh.

Each subject will receive a single SC dose of mepolizumab on Day 1 and will continue to be followed for 85 days after drug administration. On Day 1 Subjects will be observed for at least 8 hours after drug administration until they are sent home from the unit.

Treatment Arms and Duration

Subjects will be randomised to one of three treatment arms in a 1:1:1 ratio:

- 100 mg SC of the liquid drug product in safety syringe
- 100 mg SC of the liquid drug product in autoinjector
- 100 mg SC of the reconstituted lyophilised drug product

Subjects will receive 100 mg mepolizumab SC as a single injection. The randomisation will be stratified by body weight (<70kg, 70-<80kg and ≥80kg). Subjects will also be randomised in a 1:1:1 ratio to one of three injection locations: upper arm, abdomen or thigh. The selection of administration into the right or left side will be based on the preference of the subject or if no preference is expressed, the preference of the investigator.

Subjects will be screened within 30 days before dose administration.

For any given treatment arm subjects will be resident in the unit from the morning before Day 1 (Day –1) until at least 8 hours after drug administration on Day 1, after which subjects will be sent home if deemed appropriate at the discretion of the investigator. The study will include a further 15 outpatient visits at 24h (Day 2), 48h (Day 3) and on Days 4, 5, 6, 7, 8, 9, 10, 15, 22, 29, 43, 57 and 85 for PK, PD and safety evaluations. A subject will be considered having completed the study if they complete the final visit on day 85. Each subject will participate in the study for up to approximately 16 weeks (85 days after drug administration), and will have a screening visit, a single dose treatment period, and a follow-up visit.

Follow-up procedures will be performed on the day of discharge (Day 85) after the last blood sample is collected.

Type and Number of Subjects

This study will be conducted in male and female healthy subjects aged ≥18 years old.

Approximately 243 healthy subjects will be randomised resulting in at least 216 completed subjects (approximately 72 for each mepolizumab treatment, 24 per injection site). At least 27 subjects will be randomised within each of three body weight strata (<70kg, 70-<80kg and ≥80kg), resulting in at least 9 subjects randomised to each mepolizumab treatment within each weight strata and 3 subjects within each mepolizumab treatment, weight strata and injection site. Additional subjects may be enrolled if deemed appropriate to ensure at least 216 completed subjects at the discretion of the Sponsor in consultation with the Investigator. (i.e. complete Day 85 visit). See Table 1.

Table1 Study Design with treatment arms, body weight ranges and injection sites

Number of Subjects		Safety Syringe			Auto injector			Lyophilized Formulation			
		Upper Arm	Thigh	Abdomen	Upper Arm	Thigh	Abdomen	Upper Arm	Thigh	Abdomen	
Body Weight	<70 kg	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥27
	70 – <80 kg	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥27
	≥80 kg	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥27
Total		≥27			≥27			≥27			243

Analysis

The primary analysis will compare $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax for each test treatment (liquid drug product in autoinjector or liquid drug product in safety syringe) to the reference (reconstituted lyophilised drug product). The analysis for each treatment comparison will be conducted excluding the data from the test treatment that is not relevant for that comparison. The parameters $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax will be $\log_e$ transformed and analysed separately using a fixed effects model, including treatment group and injection site (upper arm, abdomen, thigh) as categorical variables and baseline weight as a continuous covariate fitted on the $\log_e$ scale. Point estimates and associated two-sided 90% confidence intervals **(CI)** will be constructed for the differences between the test and reference treatments on the $\log_e$ scale; these will be back-transformed to provide point estimates and two-sided 90% CIs for the ratio of each of the test treatments to the reference treatment on the original scale.

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

2. INTRODUCTION

2.1. Study Rationale

Mepolizumab (SB-240563) is a humanized monoclonal antibody (IgG1, kappa, mAb) that blocks human interleukin-5 (hIL-5) from binding to the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits signalling. Neutralization of IL-5 with mepolizumab reduces blood and sputum eosinophils, which results in a reduction in exacerbations/flares and in the maintenance dose of oral corticosteroids (OCS) in various eosinophilic-mediated diseases.

Mepolizumab has been investigated for the treatment of patients with severe eosinophilic asthma who have current blood eosinophil levels of 150 cells/μL or greater, or historical blood eosinophil levels (within 12 months) of 300 cells/μL or greater and history of exacerbations despite high dose inhaled corticosteroid therapy and an additional controller. It has been recently approved in a number of markets including the EU (03 December 2015) and US (04 November 2015). Mepolizumab has also been evaluated in subjects with moderate asthma, FIP1L1/PDGFRα-negative hypereosinophilic syndrome (HES), eosinophilic esophagitis (EoE) and eosinophilic granulomatosis with polyangiitis (EGPA) (i.e., Churg Strauss syndrome). Clinical data for mepolizumab administered by the **intravenous** (IV), SC or IM routes in a variety of eosinophilic conditions is summarised in the Investigators' Brochure (GlaxoSmithKline Document Number CM2003/00010/10). The liquid drug product is described in the Investigators' Brochure Supplement (GlaxoSmithKline Document Number 2016N290279_00).

Mepolizumab for Injection, a sterile, single-use, preservative-free, lyophilized drug product formulation (herein referred to as lyophilized drug product) was used in the clinical development program and is the current marketed presentation for asthma (Nucala™). Before use each vial of lyophilized drug product must be reconstituted with water for injection (WFI) using aseptic techniques. As part of the life cycle of mepolizumab, a liquid drug product provided as a ready-to-use pre-filled syringe assembled into either a safety syringe or an autoinjector, Mepolizumab Injection, has been developed. Administration of Mepolizumab Injection (herein referred to as liquid drug product in autoinjector or liquid drug product in safety syringe) will be more convenient and may allow the ultimate goal of patient self-administration. Mepolizumab Injection has not been previously administered in man.

In vitro analytical data confirms that the liquid and lyophilised formulations of mepolizumab are comparable. Consequently the likelihood of clinically significant differences in the systemic exposure, efficacy or safety profile between the liquid drug product in safety syringe or auto injector and the lyophilised drug product is considered to be low. However, in addition to demonstration of in vitro biochemical comparability, the change in formulation and the change in drug product presentation from a manually administered reconstituted lyophile to a liquid drug product (administered from a safety syringe or autoinjector) requires demonstration clinically that the relative bioavailability of the treatments are similar (ICHQ5E; biopharmaceutical comparability). A full description of the liquid drug product (safety syringe and autoinjector) is given in the

Investigators' Brochure Supplement (GlaxoSmithKline Document Number 2016N290279_00).

The aim of this study is to provide relative bioavailability data to support the transition from the currently marketed presentation of the lyophilised drug product to the liquid drug product in autoinjector and the liquid drug product in safety syringe. The study is intended to demonstrate comparable mepolizumab pharmacokinetics following a single subcutaneous (SC) dose administration in healthy subjects. Safety (including immunogenicity) and tolerability will also be evaluated. Blood eosinophil count and device functionality will also be explored.

2.2. Brief Background

Mepolizumab binds with high affinity to human IL-5 and blocks its binding to and the activation of the IL-5 receptor (CD125).

The randomized, multi-centre, placebo-controlled exacerbation studies MEA112997, MEA115588 (Pavord, 2012, Ortega, 2014) and Oral Corticosteroid (OCS) Reduction Study MEA115575 (Bel, 2014) have demonstrated the efficacy of mepolizumab and support the use of mepolizumab 100 mg SC every 4 weeks as an add-on therapy for the treatment of severe eosinophilic asthma. Compared with placebo, mepolizumab has been shown to:

- Reduce the rate of clinically significant exacerbations by approximately 50%. These results were replicated in studies MEA112997 (Pavord, 2012) and MEA115588 (Ortega, 2014).
- Reduce the rate of exacerbations requiring hospitalisations and/or Emergency Department (ED) visits, with mean reductions ranging from 32% to 61%.
- Produce statistically significant and/or clinically relevant improvements in lung function based on forced expiratory volume in one second (FEV_1), asthma control based on Asthma Control Questionnaire (ACQ-5), quality of life based on St. George's Respiratory Questionnaire (SGRQ) and clinician and subject-rated overall response to therapy in the target population.
- Produce consistent reductions in blood eosinophil levels detected at Week 4 which were sustained for the duration of treatment.

Additional details of the pharmacology, efficacy and safety can be found in the Investigator Brochure (GlaxoSmithKline Document Number 2016N290279_00).

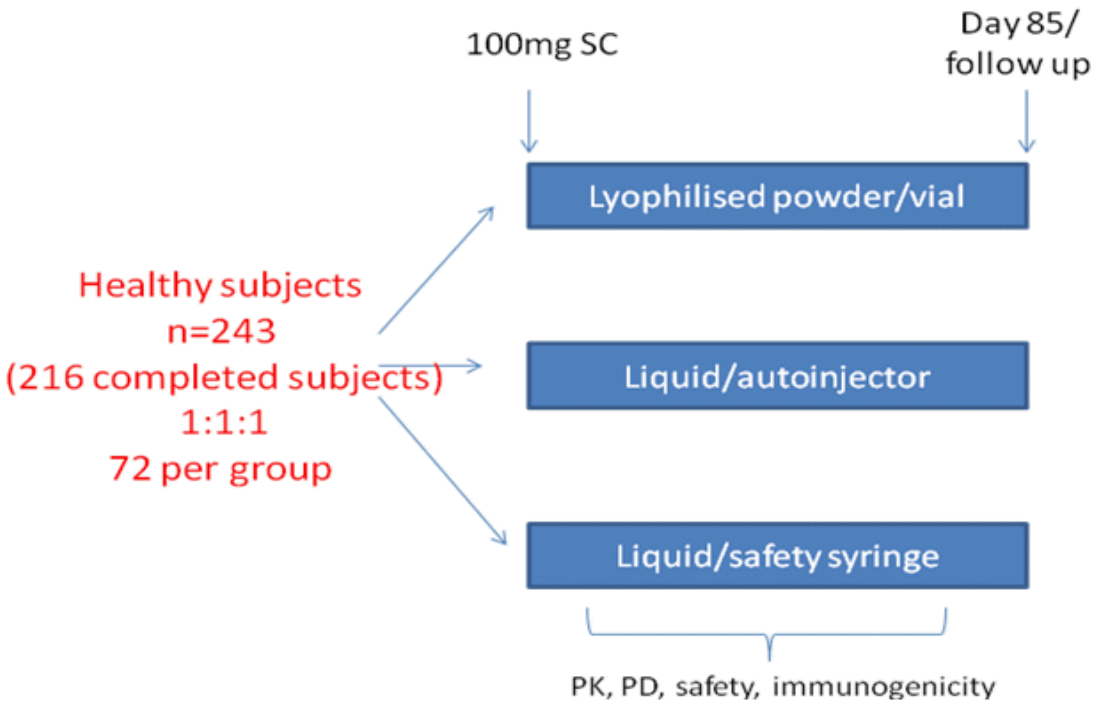
3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To compare the pharmacokinetics of subcutaneous mepolizumab following a single dose of the. liquid drug product in safety syringe with the lyophilized drug product	• Mepolizumab PK parameters: Cmax, AUC(0-t) and AUC(0-∞).
• To compare the pharmacokinetics of subcutaneous mepolizumab following a single dose of the liquid drug product in autoinjector with the lyophilized drug product.	• Mepolizumab PK parameters: Cmax, AUC(0-t) and AUC(0-∞).
Secondary	
• To assess additional pharmacokinetic parameters following mepolizumab subcutaneous administration of the liquid drug product in autoinjector or the liquid drug product in safety syringe in comparison with the lyophilized drug product, as data permit	• tmax, CL/F, Vd/F, λz, t ½, tlast, %AUCex.
• To assess the safety and tolerability of mepolizumab following a single SC dose of the liquid drug product in autoinjector or the liquid drug product in safety syringe in comparison with the lyophilised drug product	• Adverse events (AEs), serious adverse events (SAEs), including systemic reactions and injection site reactions. • Haematology and Clinical Chemistry • Vital signs • 12-lead ECG
• To assess the immunogenicity of mepolizumab following a single SC dose of the liquid drug product in autoinjector or the liquid drug product in safety syringe in comparison with the lyophilised drug product	• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies

Objectives	Endpoints
Exploratory	
• To evaluate mepolizumab pharmacodynamic effects on blood eosinophil count following a single SC dose of the liquid drug product in safety syringe or the liquid drug product in autoinjector in comparison with the lyophilised drug product	• Ratio to baseline in blood eosinophil count over time
• To evaluate safety syringe and autoinjector use & functionality	• **User and device errors**

4. STUDY DESIGN

4.1. Overall Design



This will be a randomised, multi-centre, open-label, three arm, parallel-group, single-dose study in healthy subjects. Three different mepolizumab treatments will be administered:

- a liquid drug product in a safety syringe (test),
- a liquid drug product in an autoinjector (test),
- a reconstituted lyophilised drug product from a vial (reference).

All treatments will be administered **SC** by a health care professional (HCP). The study will compare the pharmacokinetics and safety of mepolizumab administered as a liquid drug product in two different devices with the reconstituted lyophilised drug product. Blood eosinophil count and device functionality will also be explored.

Subjects will receive 100 mg mepolizumab SC as a single injection. The randomisation will be stratified by body weight (<70kg, 70-<80kg and ≥80kg). The site of injection will be randomised 1:1:1 to the upper arm, abdomen or thigh.

Each subject will receive a single SC dose of mepolizumab on Day 1 and will be observed and blood samples collected for at least 8 hours post dose until they are sent home from the unit. Subjects will continue to be followed for 85 days after drug administration.

4.2. Treatment Arms and Duration

Subjects will be randomised to one of three treatment arms in a 1:1:1 ratio:

- 100 mg SC of the liquid drug product in safety syringe
- 100 mg SC of the liquid drug product in autoinjector
- 100 mg SC of the lyophilised drug product

Subjects will receive 100 mg mepolizumab SC as a single injection. The randomisation will be stratified by body weight (<70kg, 70-<80kg and ≥80kg). The site of injection will be randomised 1:1:1 to the upper arm, abdomen or thigh. The selection of administration into the right or left side will be based on the preference of the subject or if no preference is expressed, the preference of the investigator.

Subjects will be screened within 30 days before dose administration.

For any given treatment arm subjects will be resident in the unit from the morning before Day 1 (Day –1) until at least 8 hours after drug administration on Day 1, after which subjects will be sent home if deemed appropriate at the discretion of the investigator. The study will include a further 15 outpatient visits at 24h (Day 2), 48h (Day 3) and on Days 4, 5, 6, 7, 8, 9, 10, 15, 22, 29, 43, 57 and 85 for PK, PD and safety evaluations. A subject will be considered having completed the study if they complete the final visit on day 85. Each subject will participate in the study for up to approximately 16 weeks (up to 85 days after drug administration), and will have a screening visit, a single dose treatment period, and a follow-up visit.

Follow-up procedures will be performed on the day of discharge (Day 85) after the last blood sample is collected.

4.3. Type and Number of Subjects

This study will be conducted in male and female healthy subjects aged ≥18 years old.

Approximately 243 healthy subjects will be randomised resulting in at least 216 completed subjects (approximately 72 for each mepolizumab treatment, 24 per injection

site). At least 27 subjects will be randomised within each of three body weight strata (<70kg, 70-<80kg and ≥80kg), resulting in at least 9 subjects randomised to each mepolizumab treatment within each weight strata and 3 subjects within each mepolizumab treatment, weight strata and injection site. Additional subjects may be enrolled if deemed appropriate to ensure at least 216 completed subjects at the discretion of the Sponsor in consultation with the Investigator. (i.e. complete Day 85 visit). See Table 1 below**.**

Table 1 Study Design with treatment arms, body weight ranges and injection sites.

Number of Subjects		Safety Syringe			Auto injector			Lyophilized Formulation			
		Upper Arm	Thigh	Abdomen	Upper Arm	Thigh	Abdomen	Upper Arm	Thigh	Abdomen	
Body Weight	<70 kg	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥27
	70 – <80 kg	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥27
	≥80 kg	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥3	≥27
Total		≥27			≥27			≥27			243

4.4. Design Justification

A healthy subject population is considered to be suitable for the evaluation of mepolizumab PK comparability among treatments as all treatments will be administered to the same population and any differences would therefore be detected appropriately. Healthy subjects are considered to be a suitable population for biopharmaceutical PK comparability studies and the data can be extrapolated to other populations (European Medicines Agency, (2010) Guideline on the investigation of bioequivalence.).

Mepolizumab has a prolonged half-life of approximately 3 weeks and a crossover design would require an extended washout period that would limit recruitment and likely lead to significant drop-outs and is therefore considered inappropriate. A parallel group design in healthy subjects is the typical approach for such studies with monoclonal antibodies and has been successfully used for a number of similar products.

To minimise the impact of potential confounding factors and variability, the study will be stratified by body weight as this is the main covariate of mepolizumab exposure, although the effect is not large enough to be clinically relevant. To investigate the effect of

injection site, mepolizumab will be administered by the health care provider at one of three injection sites (upper arm, abdomen or thigh). In order to prevent bias as well as maintain balance in treatment groups, the injection site will be randomised. Collection of PK samples up to Day 85 will ensure that mepolizumab plasma concentration-time profile is well described with the extrapolated portion of AUC0-∞ well below 20%.

4.5. Dose Justification

A single mepolizumab dose of 100 mg administered **SC** is selected in this study as it is the approved therapeutic dose in severe asthma and the anticipated therapeutic dose in **chronic obstructive pulmonary disease** (COPD).

A higher SC dose of 300 mg is currently being investigated in EGPA and HES patients. However, this 300 mg SC dose is delivered as multiple injections (3x100 mg) of the same presentation as the reference product in this study (reconstituted lyophilised powder in a vial) and is anticipated to be delivered as 3x100 mg of the liquid formulation. Consequently the assessment of a 100 mg SC dose in this study is considered appropriate to also support the comparability of the liquid formulation delivered via a safety syringe or an auto injector to the lyophilised powder for reconstitution at a dose of 300 mg.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with mepolizumab (SB-240563) lyophilised drug product can be found in the Investigator's Brochure **(IB).** The following section outlines the key risks, risk assessment and mitigation strategy for this protocol based on mepolizumab lyophilised drug product. The safety profile of the mepolizumab liquid drug product is anticipated to be similar to the lyophilised drug product.

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Risk of Systemic Reactions, including allergic reactions	Biopharmaceutical products administered **SC** may elicit systemic (e.g. hypersensitivity) and local site reactions. In the placebo controlled severe asthma studies both acute and delayed systemic reactions including hypersensitivity have been reported following administration of mepolizumab with incidence rates similar between mepolizumab and placebo-treated subjects: • 54/915 subjects or 6% in the mepolizumab all doses combined group • 7/263 subjects or 3% in the mepolizumab 100 mg SC group • 12/344 subjects or 3% in the mepolizumab 75 mg IV group • 20/412 subjects or 5% in the placebo group. The most common symptoms reported with any systemic reaction included headache,	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of **AE**/SAE data from ongoing studies by the **GlaxoSmithKline** (GSK) study team and/or safety review team. Customized AE and SAE case report form (eDC) utilised for targeted collection of information for systemic reactions adverse events. Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 2). Subjects remain in clinic for up to 8 hours following administration of mepolizumab to complete all assessments.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	rash, pruritus, fatigue, and dizziness. While rare, serious systemic reactions including anaphylaxis have been reported. Systemic reactions reported to date across the mepolizumab programme are summarized in the IB "Adverse events of special interest" section; see also 'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	
Injection site reactions	In the placebo controlled severe asthma (PCSA) studies the incidence of local site reactions with SC administration of mepolizumab was higher on mepolizumab 100 mg SC group (21/263 or 8%) compared to mepolizumab 75mg IV (10/344 or 3%) or placebo (13/412 or 3%). Symptoms included pain, erythema, swelling, itching, and burning sensation. Local injection site reactions reported to date across the mepolizumab program are summarized in the IB "Adverse events of special interest" section; see also Section 6 titled 'Summary of Data and Guidance for	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of **AE**/SAE data from ongoing studies by GSK study team and/or safety review team. Customized AE and SAE case report form (in the eDC) utilized for targeted collection of information for local injection site reactions adverse events.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	the Investigator'.	
Potential risk of Immunogenicity	Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralizing antibody (Nab), which have the potential to modulate pharmacokinetic (PK), pharmacodynamic (PD) or produce adverse reactions. Mepolizumab has low immunogenic potential. Both incidence and titer data from completed studies demonstrate a low risk for loss of efficacy associated with AEs and/or altered PK/PD. Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; See Section 5.4 'Clinical Immunogenicity' and a summary of immunogenicity findings in Section 6 'Other Potentially Clinically Relevant Information for the Investigator'.	Blood samples will be collected for detection of both ADA and Nab.

4.6.2. Benefit Assessment

In this study, there are no anticipated benefit for the participating subjects since these subjects are healthy subjects. The autoinjector and safety syringe will however provide a more convenient mode of delivery from previous mepolizumab administration and potentially provide patients an option to self-administer mepolizumab at home.

4.6.3. Overall Benefit:Risk Conclusion

Current data from mepolizumab preclinical and clinical development indicate the ability of mepolizumab to inhibit IL-5 leading to consistent reduction in blood eosinophils, with demonstration of clinical benefit in the treatment of conditions associated with eosinophilic inflammation, such as asthma. Data from the Phase III asthma programme with mepolizumab demonstrates, compared to placebo, a reduction in asthma exacerbations, improvements in asthma control and quality of life (as measured by the ACQ and SGRQ, respectively), improvements in lung function and a reduction in oral corticosteroid use in those subjects on chronic OCS treatment. To date, the safety profile of mepolizumab has been favourable. This study will be conducted in healthy subjects which are not expected to receive benefit from this treatment. The change in drug product presentation from a reconstituted lyophilised drug product in a vial to a liquid drug product in an autoinjector or a safety syringe is not anticipated to alter the overall safety profile of mepolizumab.

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 subject eligibility is provided in the Investigator's Brochure (number).

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

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria are met:

AGE
1. 18 years of age and over at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, vital signs, laboratory tests, and cardiac monitoring. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator agrees and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or ability to interpret study results.

WEIGHT
3. Body weight ≥ 50 kg and body mass index (BMI) within the range 19.0-30kg/m^2 (inclusive)

SEX
4. Male or Female. 5. A female subject is eligible to participate if she is not pregnant (as confirmed by a negative human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following: • Documented tubal ligation • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion • Hysterectomy • Documented Bilateral Oophorectomy • Post- menopausal females- refer to Appendix 5 for definition b. Subject is of reproductive potential and agrees to follow one of the options listed in

the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (Appendix 5) from 30 days prior to the first dose of study medication and until 16 weeks after the administration of the single dose of study medication.
INFORMED CONSENT
6. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in the protocol. The subject must be able to understand and communicate in the native language of the site, e.g. German in German sites.

5.2. Exclusion Criteria

A subject 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. ALT >1.5 xULN 2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) 4. QTcF >450 msec 5. Any clinically relevant abnormality identified at the screening medical assessment (physical examination/medical history), clinical laboratory tests, or 12-lead ECG.

CONCOMITANT MEDICATIONS
6. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John’s Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the first dose of study medication and until study completion, unless in the opinion of the investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

RELEVANT HABITS
7. History of regular alcohol consumption within 6 months of the study defined as: 8. An average weekly intake **of >14 units for females and >21 units for males**. 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. 9. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening. Limit of >500 ng/mL. 10. Involved in any activities likely to result in any significant decrease or increase in body weight during the study period (e.g. 'crash' dieting, bodybuilding).

CONTRAINDICATIONS
11. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
12. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. 13. A positive test for HIV antibody. 14. Subjects with known, pre-existing helminthes infestation within 6 months prior to Day 1. 15. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 3 months. 16. The subject 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: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 17. Exposure to more than four new chemical entities within 12 months prior to the first dosing day. 18. A positive pre-study drug/alcohol screen. 19. A vulnerable subject. Defined as individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. 20. Subjects who work for the Sponsor, CRO, or one of the study centres.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, 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).

Subjects can be re-screened if they fail screening following discussion with the GSK Medical monitor and Investigator.

5.4. Withdrawal/Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.4.1. Withdrawal from the study

If a subject withdraws from the study then the assessments in the time and events table under Section 7.1 Day 85 Withdraw (WD) column must be performed. A reason for the withdrawal from the study must be captured in the eDC.

A subject must be discontinued if any of the following criteria are met:

- Withdrawal of consent
- Lost to follow-up

A subject will also be withdrawn from the study, in consultation with the medical monitor and principal investigator, if any of the following criteria are met:

- Laboratory parameters: Clinically important changes in laboratory parameters identified
- Pregnancy: Positive pregnancy test (see Section 7.3.2). Pregnancy and pregnancy outcomes of subjects exposed to mepolizumab will be followed.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject 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. Liver Chemistry Stopping Criteria

Since this is a single dose study liver chemistry stopping criteria do not apply.

However, in case of liver event following the single dose of study treatment all required follow up assessments must be completed. Refer to Appendix 2 for complete guidance.

Liver event is defined as:

ALT≥3xULN
If ALT≥3xULN **AND bilirubin** ≥ 2xULN (>35% direct bilirubin) or **INR** >1.5, Report as an SAE.

5.4.3. QTc Stopping criteria

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

However, the following guideline applies for the protocol-specified ECG and QTc evaluations.

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility and for subsequent evaluations while on the study. This formula may not be changed or substituted once the subject has been enrolled.
- For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for subsequent evaluations while on the study.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

5.5. Subject and Study Completion

A subject will be considered having completed the study if they complete the final visit on day 85.

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

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

Mepolizumab for Injection (also referred to as lyophilised drug product in this protocol) will be supplied by GSK in a 100 mg per vial strength. Mepolizumab for Injection is a sterile, lyophilized drug product and is presented in 10 mL Type I glass, stoppered vials. The formulation contains sodium phosphate, sucrose and polysorbate 80. The vial will be reconstituted with Sterile Water for Injection just prior to use. Further details of dose preparation and administration can be found in the Clinical Investigator's Brochure (CIB) and the Study Reference Manual (SRM).

Mepolizumab Injection (also referred to as liquid drug product in this protocol) will be supplied by GSK as a fixed-dose, fully disposable pre-filled Type I glass syringe with rubber stopper, which is assembled in an autoinjector or safety syringe. Mepolizumab Injection that is assembled into a safety syringe (also referred to as liquid drug product in safety syringe in this protocol) will have a back stop and plunger rod to enable manual delivery of the drug product. Mepolizumab Injection that is assembled into an autoinjector (also referred to as liquid drug product in autoinjector in this protocol) will enable automated deliver of the drug product under the power of a spring mechanism. Both presentations of Mepolizumab Injection contain 100 mg of mepolizumab in a 1 mL volume. The formulation contains sodium phosphate, citric acid, sucrose, EDTA and polysorbate 80.

	Study Treatment: Lyophilized Drug Product	**Study Treatment: Liquid Drug Product**
Product name:	Mepolizumab (Nucala) (SB-240563)	Mepolizumab (Nucala) (SB-240563)
Description of Device:	N/A	Prefilled autoinjector Prefilled Safety Syringe
Formulation description:	100 mg/mL mepolizumab following reconstitution with 1.2 mL sterile water for injection (WFI) with sodium phosphate, sucrose, and polysorbate 80	100 mg/mL mepolizumab with sodium phosphate, citric acid, sucrose, EDTA and polysorbate 80
Dosage form:	Sterile, lyophilized powder for reconstitution	Sterile, liquid formulation
Unit dose strength(s)/ Dosage level(s):	100 mg/vial	100 mg/mL; 1.0 mL (deliverable)
Route of Administration	SC injection	SC injection
Dosing instructions:	SC dose in upper arm, abodomen, or thigh following reconstitution with 1.2 mL WFI	SC dose in upper arm, abdomen or thigh

	Study Treatment: Lyophilized Drug Product	**Study Treatment: Liquid Drug Product**
Physical description:	White, uniform, lyophilized cake. Clear to opalescent, colourless to pale yellow sterile solution after reconstitution.	Clear to opalescent, colourless to pale yellow sterile solution
Physical description of device:	N/A	**Autoinjector:** Single use, disposable autoinjector assembled with the prefilled syringe containing the drug product. The autoinjector enables automatic delivery of the drug product under the power of a spring mechanism following activation of the device. Start and end of injection clicks inform the user of correct use. A plastic needle cover shields the needle before and after injection to minimise the potential for needle stick injuries. **Safety syringe:** Single use, disposable safety syringe. Needle retracts into guard which locks.
Manufacturer/ source of procurement:	Lyophilized Drug product is manufactured at GSK, Parma, Italy	**Prefilled syringe**: Prefilled syringe components are procured from Becton Dickinson. Prefilled syringe is filled with drug product and assembled at GSK, Barnard Castle, UK. **Autoinjector:** The autoinjector components are manufactured by Ypsomed AG and assembled with the prefilled syringe at GSK, Barnard Castle, UK. **Safety syringe:** supplied pre-filled with drug. Components are procured by Becton Dickinson. Product assembled at GSK, Barnard Castle, UK.

6.2. Medical Devices

The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are injection devices: a prefilled syringe contained within an autoinjector or a prefilled syringe within a safety syringe. The devices used in the study are representative of the devices planned to be marketed for the product.

The components that comprise the prefilled syringe, including glass barrel with prestaked needle and stopper are sourced from Becton Dickinson. The prefilled syringe is filled and assembled at GSK Barnard Castle. The prefilled syringe is assembled with safety syringe device components at GSK Barnard Castle. The safety syringe components are also sourced from Becton Dickinson.

The autoinjector components are manufactured by Ypsomed AG. The auto injector components are assembled with the prefilled syringe at GSK Barnard Castle.

The instructions for use (IFU) of these injection devices are provided in the **SRM**. The instructions were developed and optimized as a result of formative human factors studies.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 7.4.

6.3. Treatment Assignment

Subjects will be assigned to one of the three treatments, reconstituted lyophilised powder from a vial, liquid formulation delivered by auto injector, liquid formulation delivered by safety syringe, in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Randomization numbers will be allocated centrally via interactive response technology (IRT). The randomisation will be stratified by body weight (<70kg, 70-<80kg and ≥80kg) measured at day -1. The site of injection will also be randomised 1:1:1 to the upper arm, abdomen or thigh.

6.4. Blinding

This will be an open-label single dose study.

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

Mepolizumab must be stored in a refrigerator or at a temperature of 2-8°C and protected from light.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) /equivalent document describing the occupational hazards of mepolizumab and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

A description of the methods and materials required for mepolizumab will be detailed in the **SRM.**

- Only subjects enrolled in the study may receive study treatment and only authorized 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 authorized 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.

Mepolizumab lyophile will be provided as a lyophilised drug product in sterile vials for individual use and should be stored in a refrigerator at 2-8°C with protection from light. The vial will be reconstituted with Sterile Water for Injection, just prior to use. Each vial will contain 100 mg mepolizumab as a single 1.0 mL injection (100 mg/mL). Maintenance of a temperature log at the clinical dispensing sites (manual or automated) is required.

Mepolizumab liquid will be supplied in a single use safety syringe and prefilled syringe contained within an autoinjector and both should be stored in a refrigerator at 2-8°C with protection from light. Each injection device will contain 100 mg mepolizumab as a single 1.0 mL injection of the liquid formulation (100 mg/mL). Maintenance of a temperature log at the clinical dispensing sites (manual or automated) is required.

6.7. Training Session

Training of qualified site personnel in study treatment handling and administration techniques at each study site will be provided by GSK prior to the first subject administration at a given site. Further details of the training will be provided in the SRM.

6.8. Compliance with Study Treatment Administration

Subjects will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic and site of administration (thigh, abdomen or upper arm) will be recorded in the source documents. The study treatment, dose and study subject 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.

In the event of an acute severe reaction (e.g., anaphylaxis) following administration of mepolizumab, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the subject including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the subject to another facility for additional care if appropriate.

6.9. Treatment of Study Treatment Overdose

The dose of mepolizumab considered to be an overdose has not been defined. There are no known antidotes and GSK does not recommend a specific treatment in the event of a suspected overdose. The investigator will use clinical judgment in treating the symptoms of a suspected overdose.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because only healthy subjects are eligible to participate in the study.

6.11. Lifestyle and/or Dietary Restrictions

6.11.1. Caffeine, Alcohol, and Tobacco

- During the dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 12 hours prior to the start of dosing until collection of the final pharmacokinetic and/or **PD** sample of the session and prior to all out-patient visits.
- During the dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and/or **PD** sample of the session and prior to all out-patient visits.
- Use of tobacco products is not allowed from 6 months prior to screening until after the final follow-up visit.

6.11.2. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during the study (e.g. read).

Subjects should abstain from any activities likely to result in any significant decrease or increase in body weight during the study period (e.g. ‘crash’ dieting, bodybuilding).

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

Concomitant medications are not allowed during this study as outlined in Section 5.2 (exclusion criteria).

Paracetamol (acetaminophen) ≤ 2g/day as a mild analgesic is allowed throughout the study. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor if required.

6.12.2. Prohibited Medications and Non-Drug Therapies

Subjects must refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

Recreational drug use is not allowed during the study.

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 (Section 7.1), 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:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws.

  Note: The timing of the assessments should allow the blood draw to occur at the nominal time as stated in the SRM.
- The timing and number of planned study assessments, including safety, pharmacokinetic, **PD**/biomarker 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 IRB/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 the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

Procedure	**Screening (up to 30 days prior to Day 1)**	**Treatment Period 1 [Days]**																**Notes: Permitted Time windows will be defined in the GSK approved Windows Allowance Agreement used by each site**
		Day -1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**15**	**22**	**29**	**43**	**57**	**85 (FUP/EW)**	
Informed consent	X																		
Inclusion and exclusion criteria	X	X																	
Demography	X																		
Full physical exam including height[1] and weight[2]	X	X																X	[1]Height only at screening [2]Weight collected only at day -1
Medical history (includes substance usage) Including Cardiovascular medical history/risk factors	X																		
Alcohol test	X	X																	Alcohol measured in Serum
Drug Screen	X	X																	Serum or Urine drug screen
Urine Cotinine test	X	X																	Tobacco

Procedure	**Screening (up to 30 days prior to Day 1)**	**Treatment Period 1 [Days]**																**Notes: Permitted Time windows will be defined in the GSK approved Windows Allowance Agreement used by each site**
		Day -1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**15**	**22**	**29**	**43**	**57**	**85 (FUP/EW)**	
Past and current medical conditions	X																		
Pregnancy test	X	X													X			X	All pregnancy tests will be performed in urine.
Laboratory assessments including haematology, chemistry and urinanalysis	X	X					X											X	Includes Liver chemistry
HIV, Hep B and Hep C screen	X																		If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Immunogenicity	X		X[3]												X	X		X	[3]Day 1 Predose. Including ADA and Nab
12-lead ECG	X		X															X	Day 1 – Predose

Procedure	**Screening (up to 30 days prior to Day 1)**	**Treatment Period 1 [Days]**																**Notes: Permitted Time windows will be defined in the GSK approved Windows Allowance Agreement used by each site**
		Day -1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**15**	**22**	**29**	**43**	**57**	**85 (FUP/EW)**	
Vital signs	X	X	X[4]	X	X	X	X	X	X							X		X	[4]Day 1 – Predose
Parasite screening	X[5]																		[5]Only required in high risk countries or for subjects who have visited high risk countries in the past six months. Sites should use local laboratories
Randomisation			X																
Study Treatment			X																Complete either the autoinjector or the safety syringe functionality assessment (see Section 7.4.4) when applicable
AE review		X	←==========→																Including local injection site reactions and systemic reactions Collected from day -1 to Day 85

Procedure	**Screening (up to 30 days prior to Day 1)**	**Treatment Period 1 [Days]**																**Notes: Permitted Time windows will be defined in the GSK approved Windows Allowance Agreement used by each site**
		Day -1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**15**	**22**	**29**	**43**	**57**	**85 (FUP/EW)**	
SAE review	X	X	←==========→																Including local injection site reactions and systemic reactions Collected from screening to Day 85
Concomitant medication review	X	X	←==========→																Collected from screening to Day 85
Blood Samples for PK			X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	[6]Day 1 – Predose, 2h & 8h Postdose
Blood samples for PD (blood eosinophils)			X[7]		X		X					X			X		X	X	[7]Day 1 – Predose
Autoinjector and safety syringe user/device error assessment			X																HCP reported. See Section 7.4.4.
Follow up (FUP)																		X	

7.2. Screening and Critical Baseline Assessments

A subject number will be assigned at the time the informed consent form (ICF) is signed. During the screening Visit, study designated personnel must provide informed consent to study participants.

Once the informed consent document has been signed, screening assessments can be conducted. The following demographic parameters will be captured: year of birth, sex, race and ethnicity. From the screening visit onwards concomitant medications and SAEs (considered as related to study participation) must be reported.

7.2.1. Critical procedures performed at Screening

- Medical history including smoking status, current treatment
- Cardiovascular medical history/risk factors (as detailed in the eDC system). This assessment must include a review of the subject responses to the cardiovascular assessment questions and height, weight, blood pressure, smoking history, medical conditions, and family history of premature cardiovascular disease.
- Physical exam
- Vital signs
- 12-lead ECG
- Laboratory tests. This should include:
    - Chemistry
    - Haematology with differential count
    - Urinalysis
    - Pregnancy test (serum)
    - FSH
    - Parasitic screening (only in countries with a high-risk or in subjects who have visited a high-risk country)
    - HIV, Hep B, Hep C screen
    - Blood for Immunogenicity
- Review of Inclusion/Exclusion criteria
- Review of SAEs

7.2.2. Critical procedures performed at first treatment visit

- Vital signs
- Blood for PK assessment
- Blood for PD assessment (pre-dose sample)
- Blood for Immunogenicity (pre-dose sample)
- 12 lead ECG
- Study treatment
- Device functionality questions
- Review concomitant medications, AEs, SAEs

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1).

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

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

- The following adverse events of special interest will have additional information (i.e. corresponding symptoms) collected via AE and SAE pages in the eDC:
- Local injection site reactions
- Systemic reactions

In addition, the information whether an event met the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] and in Appendix 6 will be collected on the AE and SAE eDC pages.

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 subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact on Day 85 (see Section 7.3.1.3), at the timepoints 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 eDC.

- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in the Time and Events Table Section 7.1.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject 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 3.

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 subject 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 subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3.

7.3.1.4. 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 subjects 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, Institutional Review Board (IRB)/Independent Ethics Committee (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

- Details of all pregnancies in female subjects will be collected after the start of dosing and until 16 weeks after last dose.
- 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 5.

7.4. Medical Device Incidents (Including Malfunctions)

GSK medical devices are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 4.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 7.3.1 and Appendix 3 of the Protocol.

7.4.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented and reported during all periods of the study in which the GSK medical devices are available for use.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a GSK medical device provided for the study, the investigator will promptly notify GSK.

NOTE: The method of documenting Medical Device Incidents is provided in Appendix 4.

7.4.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE, will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5). The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

7.4.3. Prompt Reporting of Medical Device Incidents to GSK

- Medical device incidents will be reported to GSK within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.
- Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the Medical Monitor. The same individual will be the contact for receipt of medical device reports and SAEs.
- In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.

7.4.4. Autoinjector and safety syringe functionality assessment

During administration of the autoinjector and safety syringe the HCP will be asked to inspect the medical device and complete the inspection questions in Appendix 7 and Appendix 9 respectively.

If there is an error with the medical device then refer to the Autoinjector or safety syringe Error / Failure Reporting Form in Appendix 8 or Appendix 10 respectively.

7.4.5. Returning defective Medical Devices to GSK

All defective devices will be returned to GSK

- Please refer to the SRM for all details

7.4.6. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any GSK medical device provided for use in the study in order for GSK to fulfil the legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution in Japan), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

7.5. Physical Exams

Consider further specification (e.g. for height and weight measurements, the subject is allowed to wear indoor, daytime clothing with no shoes) if appropriate to the study.

A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.

7.5.1. Vital Signs

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

7.5.2. Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- If a routine single ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTc values of the three ECGs. Refer to Section 5.4.3 for additional QTc readings that may be necessary.
- ECG measurements will be made after the subject has rested in the supine position for 5 minutes. The ECG should be obtained before the vital signs assessments and followed by other study procedures.

7.5.3. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Section 7.1, 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 subject 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 subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eDC.

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

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 2.

Table 2 Protocol Required Safety Laboratory Assessments

<table>
<tr><td>Laboratory Assessments</td><td>Parameters</td></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td>RBC Indices:</td><td>WBC count with Differential:</td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Albumin</td></tr>
<tr><td>CK</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Routine Urinalysis</td><td>• Specific gravity
• pH, glucose, protein, blood and ketones by dipstick
• Microscopic examination (if blood or protein is abnormal)
• Urine microscopic examination : RBC, WBC, Epithelial cells, Casts (hyaline, granular, cellular)</td></tr>
<tr><td>Other Screening Tests</td><td>• HIV
• Hepatitis B (HBsAg)
• Hepatitis C (Hep C antibody)
• FSH and estradiol (as needed in women of non-child bearing potential only)
• Alcohol and drug screen (to include at minimum: cotinine, amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
• Pregnancy- All tests will be performed in urine.
• Immunogenicity – Nab, ADA
• Parasitic screening – for subjects who have travelled to countries with a high-risk</td></tr>
<tr><td colspan="2">NOTES :

1. Details of Required Actions and Follow-Up Assessments after liver event are given in Section 5.4.2 and Appendix 2.</td></tr>
</table>

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study 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.

7.6. Pharmacokinetics

7.6.1. Blood Sample Collection

Blood samples for determination of mepolizumab plasma concentration will be collected at the time points indicated in Section 7.1, Time and Events Table. 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. Further details will be specified in the Study Reference Manual (SRM).

7.6.2. Sample Analysis

Plasma analysis will be performed under the control of PTS, **GSK**, the details of which will be included in the Study Reference Manual (SRM). Concentrations of mepolizumab 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 analyzed for mepolizumab any remaining plasma may be analyzed for other compound-related material and the results reported under a separate PTS, **GSK** protocol.

7.7. Pharmacodynamic Markers

Blood eosinophil counts will be recorded at the visits specified in the Time and Events Schedule (Section 7.1).

7.8. Immunogenicity

Blood samples will be collected for the determination of anti-mepolizumab antibodies, prior to dosing and as detailed in the Time and Events Schedule (Section 7.1)

Details for sample collection and processing may be found in the SRM.

8. DATA MANAGEMENT

- For this study subject data will be entered into a GSK approved database and combined with data provided from other sources in a validated data system. The data will be transmitted electronically to GSK.
- Management of clinical data will be performed in accordance with approved GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- Subject initials and full date of birth will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

This study is designed to evaluate mepolizumab PK comparability following a single SC administration, i.e. the relative bioavailability, between

- The liquid drug product from the autoinjector (test) and the reconstituted lyophilised drug product from the vial (reference)
- The liquid drug product from the safety syringe (test) and the reconstituted lyophilised drug product from the vial (reference)

For $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax, point estimates and corresponding two-sided 90% confidence intervals **(CI)** will be constructed for the ratio of the geometric mean of each test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference). No formal hypothesis will be tested. However, interpretation of the comparability of the autoinjector and safety syringe with the reconstituted lyophilised drug product will be guided by a two-sided 90% **CI** for μ(test)/μ(reference) in the range (0.80, 1.25) for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax.

9.2. Sample Size Considerations

The primary objective of this study is to evaluate the PK comparability of the liquid drug product administered by both the autoinjector and safety syringe with the lyophilised drug product when reconstituted from the vial. The sample size for this study is based on the number of subjects needed to demonstrate a two-sided 90% CI for μ(test)/μ(reference) within the guide range of (0.80, 1.25) for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$ and Cmax.

Variability estimates for $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$ and Cmax for mepolizumab were considered from three studies; SB-240563/017, SB-240563/018 and MEA114092. Only data from treatment groups with SC administration of mepolizumab in the upper arm, abdomen or thigh, for doses of 125mg and 250mg across the 3 studies was considered.

For AUC, estimates for the between subject standard deviation on the $\log_e$ scale, after adjusting for body weight, ranged from 0.18 to 0.27, with a mean (weighted by degrees of freedom) estimate of 0.222. For Cmax, estimates for the between subject standard deviation on the $\log_e$ scale, after adjusting for body weight, ranged from 0.20 to 0.32, with a mean (weighted by degrees of freedom) estimate of 0.252.

The joint power to demonstrate an observed 90% CI within the guide range (0.80, 1.25) for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax for both the autoinjector and safety syringe has been estimated using simulation. Assuming standard deviations on the $\log_e$ scale of 0.222 for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and 0.252 for Cmax (i.e. the mean estimates given above), a true difference between the formulations of 5% and a within subject correlation between AUC and Cmax of 0.8, the estimated joint power with 72 subjects per treatment group is 98%. Assuming standard deviations on the $\log_e$ scale of 0.27 for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and 0.32

for Cmax (i.e. the highest estimates given above), and with all other assumptions as above, the estimated joint power with 72 subjects per treatment group is 89%.

To allow for a dropout rate of up to 10%, approximately 243 subjects (81 per treatment group) will be enrolled in this study.

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

Final analysis will be performed after the completion of the study and final data base freeze. Complete details of the planned analysis will be documented in the Reporting and Analysis Plan (RAP).

9.3.1. Analysis Populations

9.3.1.1. All Treated Subjects Population

The 'All Treated Subjects' population will comprise all subjects who receive mepolizumab. This population will be used for all safety and tolerability, study population and exploratory analyses.

9.3.1.2. Pharmacokinetic Population

The pharmacokinetic population will comprise all subjects in the 'All Treated Subjects' population who have at least one PK sample obtained and analysed. This population will be used for all pharmacokinetic analyses, including the primary analysis.

9.3.2. Interim Analysis

No interim analyses are planned.

9.4. Key Elements of Analysis Plan

9.4.1. Raw Plasma 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 will be plotted for each treatment. Plasma concentrations of mepolizumab will be listed and summarised by treatment group and within each treatment group by weight category (<70kg, 70-<80kg and ≥80kg) and by injection site; and nominal time.

9.4.2. 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 mepolizumab will be analyzed 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 treatment and for each subject:

- maximum observed plasma concentration (Cmax)
- time to Cmax (tmax)
- area under the plasma concentration time curve [AUC(0-t), AUC(0-week4) and AUC (0-∞)]
- %AUCextrapolated
- Last time point where the concentration is above the limit of quantification (tlast)
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vd/F)
- terminal phase elimination rate constant (λz)
- the number of points used to determine λz
- the terminal phase half-life (t1/2).

Pharmacokinetic data will be presented in graphical and/or tabular form and will be listed and summarized descriptively by treatment group, and within each treatment group by weight category (<70kg, 70-<80kg and ≥80kg) and by injection site.

All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of

Clinical Statistics, GlaxoSmithKline.

9.5. Primary Analyses

The primary analysis will compare $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax for each test treatment (liquid formulation from the autoinjector or safety syringe) to the reference (reconstituted lyophilised powder from the vial). The analysis for each treatment comparison will be conducted excluding the data from the test treatment that is not relevant for that comparison. The parameters $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax will be $\log_e$ transformed and analysed separately using a fixed effects model, including treatment group and injection site (upper arm, abdomen, thigh) as categorical variables and baseline weight as a continuous covariate fitted on the $\log_e$ scale. Point estimates and associated two-sided 90% **CIs** will be constructed for the differences between the test and reference treatments on the $\log_e$ scale; these will be back-transformed to provide point estimates and two-sided 90% CIs for the ratio of each of the test treatments to the reference treatment on the original scale.

9.6. Secondary Analyses

Safety data will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. AEs will be coded using the MedDRA coding dictionary and summarized by preferred term. Separate summaries will be provided for all AEs, IP-related AEs, SAEs, events of special interest (including systemic reactions and local injection site reactions).

All laboratory parameters for clinical chemistry and haematology will be summarized and tabulated.

Each ECG parameter at every assessed time point will be summarized. Summary statistics of QT interval corrected for heart rate according to Frederica's formula (QTcF) and QT interval corrected for heart rate according to Bazett's formula (QTcB) as well as change from baseline values will be presented by time point.

Summary statistics of pulse rate and systolic and diastolic blood pressure will be presented by time point.

Immunogenicity will be summarized using appropriate descriptive statistics.

9.6.1. Exploratory Analyses

Ratio to baseline in blood eosinophil count will be log transformed and compared between treatments using a mixed model repeated measures analysis, adjusting for the covariates of baseline blood eosinophil count (log scale) and baseline weight (log scale). Time point and injection site (upper arm, abdomen, thigh) will be fitted as a categorical variables with the effect of treatment group and baseline blood eosinophil count varying at each timepoint (i.e. timepoint-by-baseline and timepoint-by-treatment interactions will be included in the model).

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

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 enrollment of subjects 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 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 Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the 1996 version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable 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 for each subject 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 eDC system 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 subjects 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 multicenter 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 Publically 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 subjects, 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.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ACQ-5	Asthma Control Questionnaire
ADA	Anti Drug Antibody
AE	Adverse Event
AUC	Area Under the Concentration-Time Curve
AUC(0-week4)	Area Under the Concentration-Time Curve from Time Zero (pre-dose) to Week 4
AUC(0-t)	Area Under the Concentration-Time Curve from Time Zero (pre-dose) to Last Time of Quantifiable Concentration
AUC(0-∞)	Area Under the Concentration-Time Curve from Time Zero Extrapolated to Infinite Time
%AUCex	Percentage of AUC(0-∞) Obtained by Extrapolation
AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
CL/F	Apparent Clearance Following Subcutaneous Dosing
Cmax	Maximum Observed Concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
eDC	Electronic data capture
EGPA	Eosinophilic granulomatosis with polyangiitis
EOE	Eosinophilic esophagitis
ECG	Electrocardiogram
FEV1	Forced Expiratory volume in 1 second
FRP	Females of Reproductive potential
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HCP	Healthcare Provider
hCG	Human chorionic gonadotrophin
HES	Hypereosinophilic syndrome
IB	Investigator's Brochure
IDSL	Integrated Data Standards Library
IL	Interleukin
IV	Intravenous
λz	Terminal Phase Elimination Rate Constant
Nab	Neutralising antibody
OCS	Oral corticosteroids
PK	Pharmacokinetic
PD	Pharmacodynamic
SAE	Serious Adverse Event
SC	Subcutaneous

SGRQ	St George's Respiratory Questionnaire
SRM	Study reference manual
tlast	Time of Last Observed Concentration
tmax	Time to Cmax
t½	Terminal Phase Half-life
Vd/F	Apparent Volume of Distribution Following Subcutaneous Dosing
WCBP	Women of child bearing potential
WFI	Water For Injection

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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WinNonlin

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

Liver chemistry stopping criteria for healthy volunteers and required follow up assessments

Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Since this is a single dose study liver chemistry stopping criteria do not apply. However, in case of liver event following the single dose of study treatment (defined as liver stopping event in table below) all required follow up assessments must be completed.

Liver chemistry stopping criteria and required follow up assessments

<table>
<tr><td colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</td></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><td colspan="2">Required Actions and Follow up Assessments following Liver Stopping Event</td></tr>
<tr><td>Actions</td><td>Follow Up Assessments</td></tr>
<tr><td>Report the event to GSK within 24 hours
Complete the liver event eDC, 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 subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs</td><td>Viral hepatitis serology3
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 mepolizumab leads to lowering of eosinophils.
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.</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline A specialist or hepatology consultation is recommended If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	Record alcohol use on the liver event alcohol intake case report form If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5: Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eDC forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

References

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

12.3. Appendix 3 - Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting 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). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT 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 subject'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 subject'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.

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 subject 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 subject 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 fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in 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, diarrhea, 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 jeopardize the subject 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 subjects 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

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 eDC • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE eDC page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject 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. • Subject-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.

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 subject, 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 utilized 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 Investigator Brochure (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 subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed eDC. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Reporting of SAEs to GSK

SAE reporting to GSK via paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail • Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

12.4. Appendix 4 - Definition of and Procedures for Documenting Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.2 for the list of GSK medical devices).

Medical Device Incident Definition:

- Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health.
- Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

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

A serious deterioration in state of health can include:

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

Examples of incidents

- a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse
- a patient's treatment is interrupted or compromised by a medical device failure
- misdiagnosis due to medical device failure leads to inappropriate treatment
- a patient's health deteriorates due to medical device failure

Documenting Medical Device Incidents

Medical Device Incident Documenting:

- Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE form will be completed as described in Appendix 3.
- The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK.
- It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

12.5. Appendix 5 - Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

Definition of post menopausal female

Post menopausal female is defined as:

- Females 60 years of age or older
- Menopause is the phase associated with complete cessation of menstrual cycles and implies the loss of reproductive potential by ovarian failure. This typically occurs around 50 years of age, although it may occur earlier or later. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years, in the absence of hormone replacement therapy (HRT) or medical suppression of the menstrual cycle (e.g., leuprolide treatment).
    - In questionable cases for women < 60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's postmenopausal reference range is confirmatory (these levels need to be adjusted for specific laboratories/assays) [Kronenberg, 2008; Strauss, 2004].
    - Females under 60 years of age, who are on HRT and wish to continue, and whose menopausal status is in doubt, are required to use a highly effective method to avoid pregnancy, as outlined in the protocol. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a highly effective method to avoid pregnancy. If laboratory values for FSH and estradiol are drawn and the results do not confirm menopause on a potential subject that otherwise met the specifications for being post-menopausal defined above without question, the subject may still enrol in the study as a FNRP if approved by the GSK Medical Monitor and the safety physician.

Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, 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 subjects understand how to properly use these methods of contraception.

Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, 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 subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, 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 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

12.6. Appendix 6 - Anaphylaxis Criteria

Hypersensitivity reactions will be monitored using the diagnostic criteria for anaphylaxis as outlined by the Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006]. The criteria do not make a distinction based on underlying mechanism. These criteria are summarized as follows:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
- Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

- Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
- Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

Reduced BP after exposure to known allergen for that patient (minutes to several hours):

- Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
- Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline.

12.7. Appendix 7- Inspection of the Autoinjector

Injection Assessment - Autoinjector	
Was the full dose successfully administered?	☐ Yes, injection successful
	☐ No, injection not successful (please complete the questions below [1])
	☐ No, injection not attempted
	Were there any observations with respect to the user tasks that indicate that the full dose has not been administered? Check all that apply. - Incorrect injection site selected, *record location below* _____ - Pen was not pushed all the way down and held - Pen pulled away before end of injection (i.e., before the second click, or before the plunger stops moving and the yellow indicator fills the window, or before holding for a total of 15seconds) - Evidence of liquid leaking from injection site (i.e. potentially indicating a premature lift or a wet injection) - *Other (please specify below)* _____ Were there any observations with respect to the device that indicate that the full dose has not been dispensed? Check all that apply. - Pen leaking - Components broken / cracked - Cannot push the needle guard down to activate (i.e., force required is too high) - Pen does not activate (after pressing needle guard down) - Delivery stops before end of injection (yellow indicator stopped before reaching bottom of inspection window) - *Other (please specify below)* _____

Footnote 1 refers to the Autoinjector Error / Failure Reporting Form, Appendix 8. Failure in either of these two events requires the appropriate form to be completed.

HCP should review the user tasks in completing the injection, the device and the packaging and complete Appendix 8 to capture any issues.

12.8. Appendix 8 - Auto injector Error/Failure reporting form

AUTOINJECTOR ERROR / FAILURE REPORTING FORM

Please write clearly using BLOCK CAPITAL LETTERS.

Please complete form within 24 hours of autoinjector failure/user error at site and submit to GSK

<table>
<tr><td>Primary Investigator:</td><td>Protocol #:

204958</td></tr>
<tr><td>Site Contact for IP Accountability:</td><td>Site #:</td></tr>
<tr><td>Contact Phone (print clearly):</td><td>Subject #:</td></tr>
<tr><td>E-mail (print clearly):</td><td>Autoinjector Kit #:</td></tr>
<tr><td rowspan="2">Site Address:</td><td>Date Dispensed:</td></tr>
<tr><td>Date Returned:</td></tr>
<tr><td colspan="2">Has the autoinjector been used by the HCP? ___ No ___ Yes

(Considered a biohazard.)</td></tr>
<tr><td colspan="2">Was there an AE or SAE associated with this failure/error? ___ No ___ Yes

If yes, please enter the eDC AE sequence number:_____</td></tr>
<tr><td colspan="2">Description of user error:</td></tr>
<tr><td colspan="2">Which of the following user errors apply? Tick all that apply:

__ Did not check Expiration Date

__ Incorrect preparation or incorrect choice of injection site

__ Did not check product solution

__ Clear cap not removed from autoinjector</td></tr>
</table>

__ Autoinjector not properly activated on injection site (e.g., needle guard not flush with skin) __ Autoinjector used upside down __ Autoinjector pulled away before end of injection (i.e., before yellow indicator stopped moving) __ Did not check inspection window for yellow indicator __ Other (please specify below).
Description of failure:
Reason for Autoinjector Failure. Tick all that apply: __ Autoinjector leaking __ Components broken/cracked/missing __ Inspection window not clear __ Cannot remove clear cap __ Bent needle __ Liquid is cloudy, discoloured or contains large particles __ Cannot push the needle guard down to activate (i.e., force is too high) __ Autoinjector does not activate (after pressing needle guard down) __ Delivery stops before end of injection (yellow indicator stopped before reaching bottom of inspection window) __ Other (please specify below)
Description of failure:

<table>
<tr><td colspan="2">Packaging Failure. Tick all that apply:

__ Device damaged

__ Packaging damaged or can't read label

__ Security seal was broken

__ Autoinjector missing from kit

__ Other (please specify below)</td></tr>
<tr><td>Failure Outcome (check one):

☐ Subject received no dose

☐ Subject received a partial dose
(ensure date used is captured above)</td><td>Resolution (check one) :

☐ Replacement autoinjector provided

☐ Dose omitted

☐ Subject Withdrawn</td></tr>
<tr><td>Replacement Autoinjector Dispensed Date:</td><td>Kit # of Replacement Autoinjector:</td></tr>
</table>

Instructions for further processing: Please fax or email completed Form to The GSK Pen Failure Processing Team at PPD or email address. Please contact your study monitor with any questions or for troubleshooting. Maintain the Form and in the patients' records. You may be contacted further concerning the malfunctioned autoinjector.

12.9. Appendix 9 - Inspection of the Safety Syringe

Injection Assessment – Safety Syringe	
Was the full dose successfully administered?	☐ Yes, injection successful
	☐ No, injection not successful (please complete the questions below [1])
	☐ No, injection not attempted
	Were there any observations with respect to the user tasks that indicate that the full dose has not been administered? Check all that apply. - Incorrect injection site selected, *record location below* _____ - Needle not fully inserted into site - Plunger not slowly pushed down - Plunger not pushed all the way down until the stopper reaches the bottom of the syringe - Thumb not moved up, plunger not risen and needle guard not activated - Evidence of liquid leaking from injection site (i.e. potentially indicating a premature lift or a wet injection) - *Other (please specify below)* _____ Were there any observations with respect to the device that indicate that the full dose has not been dispensed? Check all that apply. - Syringe leaking - Components broken / cracked - Cannot push the plunger rod down (i.e., required force is too high) - *Other (please specify below)* _____

Footnote 1 refers to the Safety Syringe Error / Failure Reporting Form, Appendix 10. Failure in either of these two events requires the appropriate form to be completed.

HCP should review the user tasks in completing the injection, the device and the packaging and complete Appendix 10 to capture any issues.

12.10. Appendix 10 - Safety Syringe Error/ Failure reporting form

SAFTEY SYRINGE ERROR / FAILURE REPORTING FORM

Please write clearly using BLOCK CAPITAL LETTERS.

Please complete form within 24 hours of safety syringe failure/user error at site and submit to GSK

<table>
<tr><td>Primary Investigator:</td><td>Protocol #:

204958</td></tr>
<tr><td>Site Contact for IP Accountability:</td><td>Site #:</td></tr>
<tr><td>Contact Phone (print clearly):</td><td>Subject #:</td></tr>
<tr><td>E-mail (print clearly):</td><td>Safety Syringe Number:</td></tr>
<tr><td rowspan="2">Site Address:</td><td>Date Dispensed:</td></tr>
<tr><td>Date Returned:</td></tr>
<tr><td colspan="2">Has the safety syringe been used by the HCP? ___ No ___ Yes

(Considered a biohazard.)</td></tr>
<tr><td colspan="2">Was there an AE or SAE associated with this failure/error? ___ No ___ Yes

If yes, please enter the eDC AE sequence number:_____</td></tr>
<tr><td colspan="2">Description of user error:</td></tr>
<tr><td colspan="2">Which of the following user errors apply? Tick all that apply:

__ Did not check Expiration Date

__ Incorrect preparation or incorrect choice of injection site

__ Did not check product solution</td></tr>
</table>

__ Needle shield not removed from safety syringe __ Safety syringe pulled away before end of injection (i.e., before the plunger all the way down) __ Did not check inspection window for white plunger __ Other (please specify below).
Description of failure:
Reason for Safety Syringe Failure. Tick all that apply: __ Safety Syringe leaking __ Components broken/cracked __ Inspection window not clear __ Cannot remove needle shield __ Bent needle __ Liquid is cloudy, discoloured or contains large particles __ Cannot push the plunger rod down (i.e., force is too high) __ Other (please specify below)
Description of failure:
Packaging Failure. Tick all that apply:

__ Device damaged __ Packaging damaged or can't read label __ Security seal was broken __ Other (please specify below)	
Failure Outcome (check one): ☐ Subject received no dose ☐ Subject received a partial dose (*ensure date used is captured above)*	Resolution (check one) : ☐ Replacement safety syringe provided ☐ Dose omitted ☐ Subject Withdrawn
Replacement Safety Syringe Dispensed Date:	Replacement Safety Syringe Number:

Instructions for further processing: Please fax or email completed Form to The GSK Pen Failure Processing Team at PPD or email address. Please contact your study monitor with any questions or for troubleshooting. Maintain the Form and in the subjects' records. You may be contacted further concerning the malfunctioned safety syringe.

12.11. Appendix 11 - Country Specific Requirements

No country-specific requirements exist.

12.12. Appendix 12 - Protocol Amendment Changes 01

Where this amendment Applies

This amendment applies across any site that will be used in the study.

Summary of Amendment Changes with Rationale

Change in medical monitor sponsor page. Removal of Cardiovascular and deaths events Section 7.3.1.4.

Update to the content of the error/failure reporting forms to reflect consistency with other data captured in similar studies.

List of Specific Changes

Title: Medical Monitor Page

PREVIOUS TEXT

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	Site Address
Primary Medical Monitor	PPD	Telephone: PPD PPD	Cell: PPD PPD	GlaxoSmithKline Upper Merion 709 Swedeland Road, King of Prussia, PA – 19406, USA
Secondary Medical Monitor	PPD	Telephone: PPD PPD	Cell: PPD PPD	GlaxoSmithKline 5 Moore Drive, PO Box 13398, Research Triangle Park (RTP), NC 27709-3398, USA
SAE contact information	Medical monitor as above	Telephone: PPD PPD	Cell: PPD PPD	GlaxoSmithKline 5 Moore Drive, PO Box 13398, Research Triangle Park (RTP), NC 27709-3398, USA

REVISED TEXT

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	Site Address
Primary Medical Monitor	PPD	Telephone: PPD PPD	Cell: PPD PPD	GlaxoSmithKline Upper Merion 709 Swedeland Road, King of Prussia, PA – 19406, USA
Secondary Medical Monitor	PPD	Telephone: PPD PPD	Cell: PPD PPD	GlaxoSmithKline 5 Moore Drive, PO Box 13398, Research Triangle Park (RTP), NC 27709-3398, USA
SAE contact information	Medical monitor as above	Telephone: PPD PPD	Cell: PPD PPD	GlaxoSmithKline Upper Merion 709 Swedeland Road, King of Prussia, PA – 19406, USA

Title: Updated Exploratory endpoints in Section 3 Objectives and Endpoints

PREVIOUS TEXT

Exploratory	
• To evaluate mepolizumab pharmacodynamic effects on blood eosinophil count following a single SC dose of the liquid drug product in safety syringe or the liquid drug product in autoinjector in comparison with the lyophilised drug product	• Ratio to baseline in blood eosinophil count over time
• To evaluate safety syringe and autoinjector use & functionality	• **Device functionality questions**

REVISED TEXT

Exploratory	
• To evaluate mepolizumab pharmacodynamic effects on blood eosinophil count following a single SC dose of the liquid drug product in safety syringe or the liquid drug product in autoinjector in comparison with the lyophilised drug product	• Ratio to baseline in blood eosinophil count over time
• To evaluate safety syringe and autoinjector use & functionality	• **User and device errors**

Title: Updated Section 5.4.1 Withdrawal from the study

PREVIOUS TEXT

5.4.1 Withdrawal from the study

A subject must be discontinued if any of the following criteria are met:

- Withdrawal of consent
- Lost to follow-up

A subject will also be withdrawn from the study, in consultation with the medical monitor and principal investigator, if any of the following criteria are met:

- Laboratory parameters: Clinically important changes in laboratory parameters identified
- Pregnancy: Positive pregnancy test (see Section 7.3.2). Pregnancy and pregnancy outcomes of subjects exposed to mepolizumab will be followed.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

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

- Should the subject 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".

If a subject withdraws from the study then the assessments in the time and events table under Section 7.1 Day 85 Withdraw (WD) column must be performed. A reason for the withdrawal from the study must be captured in the eDC.

REVISED TEXT

Section 5.4.1

If a subject withdraws from the study then the assessments in the time and events table under Section 7.1 Day 85 Withdraw (WD) column must be performed. A reason for the withdrawal from the study must be captured in the eDC.

A subject must be discontinued if any of the following criteria are met:

- Withdrawal of consent
- Lost to follow-up

A subject will also be withdrawn from the study, in consultation with the medical monitor and principal investigator, if any of the following criteria are met:

- Laboratory parameters: Clinically important changes in laboratory parameters identified
- Pregnancy: Positive pregnancy test (see Section 7.3.2). Pregnancy and pregnancy outcomes of subjects exposed to mepolizumab will be followed.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject 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".

Title: Update to title of procedure name in Section 7.1 Time and events table

PREVIOUS TEXT:

Autoinjector and safety syringe functionality assessment			X															HCP reported. See Section 7.4.4.

REVISED TEXT:

Autoinjector and safety syringe user/device error assessment			X															HCP reported. See Section 7.4.4.

Title: Removal of Cardiovascular and death events section

PREVIOUS TEXT

7.3.1.4 Cardiovascular and Death Events

7.3.1.4.1 Cardiovascular events

Cardiovascular-related AEs and SAEs that will require the investigator to complete event specific pages in the eDC system are listed in Section 12.3, Appendix 3.

Cardiovascular events information should be recorded on the corresponding eDC pages within one week of when the AE/SAE(s) are first reported. Please refer to Appendix 3 for timelines for reporting AE/SAEs.

7.3.1.4.2 Deaths

In addition, all deaths will require completion of a specific death data collection page in the eDC system. The death data collection page in the eDC system includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

Death information should be recorded on the death eDC system page within one week of when the death is first reported.

Please refer to Section 12.3, Appendix 3 for timelines for reporting SAEs.

REVISED TEXT

7.3.1.4 Cardiovascular and Death Events

No cardiovascular or death events will be captured in this study as this is a healthy volunteer study.

Title: Section 9.6.1 Update to the name of the device error

PREVIOUS TEXT

9.6.1 Exploratory Analyses

Ratio to baseline in blood eosinophil count will be log transformed and compared between treatments using a mixed model repeated measures analysis, adjusting for the covariates of baseline blood eosinophil count (log scale) and baseline weight (log scale). Time point and injection site (upper arm, abdomen, thigh) will be fitted as a categorical variables with the effect of treatment group and baseline blood eosinophil count varying at each timepoint (i.e. timepoint-by-baseline and timepoint-by-treatment interactions will be included in the model).

Device functionality questionnaire will be summarized using appropriate descriptive statistics.

REVISED TEXT

9.6.1 Exploratory Analyses

Ratio to baseline in blood eosinophil count will be log transformed and compared between treatments using a mixed model repeated measures analysis, adjusting for the covariates of baseline blood eosinophil count (log scale) and baseline weight (log scale). Time point and injection site (upper arm, abdomen, thigh) will be fitted as a categorical variables with the effect of treatment group and baseline blood eosinophil count varying at each timepoint (i.e. timepoint-by-baseline and timepoint-by-treatment interactions will be included in the model).

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

Title: Removal of Definition of Cardiovascular Events

PREVIOUS TEXT

Appendix 3- Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eDC 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

REVISED TEXT

This section has been removed from Appendix 3.

Title: Update to Appendix 7 Inspection of the autoinjector

PREVIOUS TEXT

Appendix 7- Inspection of the Autoinjector

INSPECTION OF AUTOINJECTOR	
Does Yellow Indicator fill the inspection window?	☐ Yes
	☐ No[1]
Has the Needle Guard locked into place? Check by pressing yellow Needle Guard against a firm surface	☐ Yes
	☐ No[1]

Footnote 1 refers to the Autoinjector Error / Failure Reporting Form, Appendix 8.
Failure in either of these two events requires the appropriate form to be completed.

REVISED TEXT

Appendix 7- Inspection of the Autoinjector

Injection Assessment - Autoinjector	
Was the full dose successfully administered?	☐ Yes, injection successful
	☐ No, injection not successful (please complete the questions below [1])
	☐ No, injection not attempted
	Were there any observations with respect to the user tasks that indicate that the full dose has not been administered? Check all that apply. - Incorrect injection site selected, *record location below* _____ - Pen was not pushed all the way down and held - Pen pulled away before end of injection (i.e., before the second click, or before the plunger stops moving and the yellow indicator fills the window, or before holding for a total of 15seconds) - Evidence of liquid leaking from injection site (i.e. potentially indicating a premature lift or a wet injection) - *Other (please specify below)* _____ Were there any observations with respect to the device that indicate that the full dose has not been dispensed? Check all that apply. - Pen leaking - Components broken / cracked - Cannot push the needle guard down to activate (i.e., force required is too high) - Pen does not activate (after pressing needle guard down) - Delivery stops before end of injection (yellow indicator stopped before reaching bottom of inspection window) - *Other (please specify below)* _____

Footnote 1 refers to the Autoinjector Error / Failure Reporting Form, Appendix 8. Failure in either of these two events requires the appropriate form to be completed.

HCP should review the user tasks in completing the injection, the device and the packaging and complete Appendix 8 to capture any issues.

Title: Update to Appendix 8 Auto injector Error/Failure reporting form

PREVIOUS TEXT

AUTOINJECTOR ERROR / FAILURE REPORTING FORM

Please write clearly using BLOCK CAPITAL LETTERS.

Please complete form within 24 hours of autoinjector failure/user error at site and submit to GSK

Primary Investigator:	Protocol #: 204958
Site Contact for IP Accountability:	Site #:
Contact Phone (print clearly):	Subject #:
E-mail (print clearly):	Autoinjector Kit #:
Site Address:	Date Dispensed:
	Date Returned:
Has the autoinjector been used by the HCP? ___ No ___ Yes (Considered a biohazard.)	
Was there an AE or SAE associated with this failure/error? ___ No ___ Yes If yes, please enter the eDC AE sequence number:_____	
Description of user error:	
Which of the following user errors apply? Tick all that apply: __ Did not check Expiration Date	

__ Incorrect preparation or incorrect choice of injection site __ Did not check product solution __ Clear cap not removed from autoinjector __ Autoinjector not properly activated on injection site (e.g., needle guard not flush with skin) __ Autoinjector used upside down __ Autoinjector pulled away before end of injection (i.e., before yellow indicator stopped moving) __ Did not check inspection window for yellow indicator __ Other (please specify below).
Description of failure:
Reason for Autoinjector Failure. Tick all that apply: __ Autoinjector leaking __ Components broken/cracked/missing __ Inspection window not clear __ Cannot remove clear cap __ Bent needle __ Liquid is cloudy, discoloured or contains large particles __ Cannot push the needle guard down to activate (i.e., force is too high) __ Autoinjector does not activate (after pressing needle guard down) __ Delivery stops before end of injection (yellow indicator stopped before reaching bottom of inspection window) __ Other (please specify below)
Description of failure:

Packaging Failure. Tick all that apply: __ Device damaged __ Packaging damaged or can't read label __ Security seal was broken __ Autoinjector missing from kit __ Other (please specify below)	
Failure Outcome (check one): ☐ Subject received no dose ☐ Subject received a partial dose (*ensure date used is captured above)*	Resolution (check one) : ☐ Replacement autoinjector provided ☐ Dose omitted ☐ Subject Withdrawn
Replacement Autoinjector Dispensed Date:	Kit # of Replacement Autoinjector:

Instructions for further processing: Please fax or email completed Form to The GSK Pen Failure Processing Team at PPD or email address. Please contact your study monitor with any questions or for troubleshooting. Maintain the Form and in the patients' records. You may be contacted further concerning the malfunctioned autoinjector.

REVISED TEXT

AUTOINJECTOR (PEN) ERROR / FAILURE REPORTING FORM

***Please write clearly using* BLOCK CAPITAL LETTERS.**

Please complete form within 24 hours of pen failure/user error at site and submit to GSK

via email to PPD

Primary Investigator:	**Protocol #:** **204958**
Site Contact for IP Accountability:	**Site #:**
Contact Phone (print clearly):	**Subject #:**

E-mail (print clearly):	
Site Address:	**Date Dispensed:**
	Date Returned:
Has the pen been used by the patient? ___ No ___ Yes (Considered a biohazard.)	
Was there an AE or SAE associated with this failure/error? ___ No ___ Yes **If yes, please enter the eCRF AE sequence number:_____**	
Please provide overall description of user/pen/packaging error/failure:	

Which of the following user errors apply? Tick all that apply:

__ Did not check expiration date

__ Did not check product solution

__ Incorrect choice of injection site

__ Clear needle cap not removed from autoinjector

__ Took longer than 5 minutes before carrying out the injection

__ Pen not properly activated on injection site (e.g., needle guard not flush with skin)

__ Pen used upside down

__ Pen not pressed and held down

__ Pen pulled away before end of injection (i.e., before the second click, or before the yellow indicator stopped moving, or

before holding for a total of 15seconds)

__ Evidence of liquid leaking from injection site (i.e. potentially indicating a premature lift or a wet injection)

__ *Other* (*please specify below*).
Description of other user error:
Reason for pen failure. Tick all that apply: __ Pen leaking __ Components broken / cracked __ Liquid is cloudy, discoloured or contains large particles __ Cannot remove clear needle cap __ Bent needle __ Cannot push the needle guard down to activate (i.e., force required is too high) __ Pen does not activate (after pressing needle guard down) __ Delivery stops before end of injection (yellow indicator stopped before reaching bottom of inspection window) __ *Other* (*please specify below*)
Description of other pen failure:
Packaging failure. Tick all that apply: __ Device damaged __ Packaging damaged or can't read label __ Security seal was broken __ Pen missing from kit __ *Other* (*please specify below*)

Description of other packaging failure:	
Error/failure outcome (check one): ☐ Subject received no dose ☐ Subject received a partial dose (*ensure date used is captured above)*	**Resolution (check one) :** ☐ Replacement pen provided ☐ Dose omitted ☐ Subject withdrawn
Replacement Pen Dispensed Date:	

Instructions for further processing: Please email completed Form to The GSK Pen Failure Processing Team at PPD Please contact your study monitor with any questions or for troubleshooting. Maintain the Form and in the subjects' records. You may be contacted further concerning the malfunctioned pen.

Title: Appendix 9: Inspection of the safety syringe

PREVIOUS TEXT

Appendix 9 - Inspection of the Safety Syringe

INSPECTION OF SAFETY SYRINGE	
Has the white plunger rod travelled down the length of the syringe?	☐ Yes ☐ No[1]
Has the Needle shield locked into place? Check by pressing clear colourless Needle shield against a firm surface	☐ Yes ☐ No[1]

Footnote 1 refers to the Safety Syringe Error / Failure Reporting Form, Appendix 10. Failure in either of these two events requires the appropriate form to be completed.

REVISED TEXT

Appendix 9 - Inspection of the Safety Syringe

Injection Assessment – Syringe	
Was the full dose successfully administered?	☐ Yes, injection successful
	☐ No, injection not successful (please complete the questions below [1])
	☐ No, injection not attempted
	Were there any observations with respect to the user tasks that indicate that the full dose has not been administered? Check all that apply. - Incorrect injection site selected, *record location below* _____ - Needle not fully inserted into site - Plunger not slowly pushed down - Plunger not pushed all the way down until the stopper reaches the bottom of the syringe - Thumb not moved up, plunger not risen and needle guard not activated - Evidence of liquid leaking from injection site (i.e. potentially indicating a premature lift or a wet injection) - *Other (please specify below)* _____ Were there any observations with respect to the device that indicate that the full dose has not been dispensed? Check all that apply. - Syringe leaking - Components broken / cracked - Cannot push the plunger rod down (i.e., required force is too high) - *Other (please specify below)* _____

Footnote 1 refers to the Safety Syringe Error / Failure Reporting Form, Appendix 10. Failure in either of these two events requires the appropriate form to be completed.

HCP should review the user tasks in completing the injection, the device and the packaging and complete Appendix 10 to capture any issues.

Title: Update to Appendix 10 Safety Syringe Error/Failure reporting form

PREVIOUS TEXT

SAFTEY SYRINGE ERROR / FAILURE REPORTING FORM

Please write clearly using BLOCK CAPITAL LETTERS.

Please complete form within 24 hours of safety syringe failure/user error at site and submit to GSK

<table>
<tr><td>Primary Investigator:</td><td>Protocol #:

204958</td></tr>
<tr><td>Site Contact for IP Accountability:</td><td>Site #:</td></tr>
<tr><td>Contact Phone (print clearly):</td><td>Subject #:</td></tr>
<tr><td>E-mail (print clearly):</td><td>Safety Syringe Number:</td></tr>
<tr><td rowspan="2">Site Address:</td><td>Date Dispensed:</td></tr>
<tr><td>Date Returned:</td></tr>
<tr><td colspan="2">Has the safety syringe been used by the HCP? ___ No ___ Yes

(Considered a biohazard.)</td></tr>
<tr><td colspan="2">Was there an AE or SAE associated with this failure/error? ___ No ___ Yes

If yes, please enter the eDC AE sequence number:_____</td></tr>
<tr><td colspan="2">Description of user error:</td></tr>
<tr><td colspan="2">Which of the following user errors apply? Tick all that apply:

__ Did not check Expiration Date

__ Incorrect preparation or incorrect choice of injection site

__ Did not check product solution

__ Needle shield not removed from safety syringe

__ Safety syringe pulled away before end of injection (i.e., before the plunger all the way down)</td></tr>
</table>

__ Did not check inspection window for white plunger __ Other (please specify below).
Description of failure:
Reason for Safety Syringe Failure. Tick all that apply: __ Safety Syringe leaking __ Components broken/cracked __ Inspection window not clear __ Cannot remove needle shield __ Bent needle __ Liquid is cloudy, discoloured or contains large particles __ Cannot push the plunger rod down (i.e., force is too high) __ Other (please specify below)
Description of failure:
Packaging Failure. Tick all that apply: __ Device damaged __ Packaging damaged or can't read label __ Security seal was broken __ Other (please specify below)

Failure Outcome (check one):	Resolution (check one) :
☐ Subject received no dose ☐ Subject received a partial dose (*ensure date used is captured above)*	☐ Replacement safety syringe provided ☐ Dose omitted ☐ Subject Withdrawn

Replacement Safety Syringe Dispensed Date:	Replacement Safety Syringe Number:

Instructions for further processing: Please fax or email completed Form to The GSK Pen Failure Processing Team at PPD or email address. Please contact your study monitor with any questions or for troubleshooting. Maintain the Form and in the subjects' records. You may be contacted further concerning the malfunctioned safety syringe.

REVISED TEXT

SYRINGE ERROR / FAILURE REPORTING FORM

Please write clearly using BLOCK CAPITAL LETTERS.

Please complete form within 24 hours of safety syringe failure/user error at site and submit to GSK

via email to PPD

Primary Investigator:	**Protocol #:** **204958**
Site Contact for IP Accountability:	**Site #:**
Contact Phone (print clearly):	**Subject #:**
E-mail (print clearly):	
Site Address:	**Date Dispensed:**
	Date Returned:
Has the safety syringe been used by the patient? ___ No ___ Yes (Considered a biohazard.)	
Was there an AE or SAE associated with this failure/error? ___ No ___ Yes **If yes, please enter the eCRF AE sequence number:**_____	
Please provide overall description of user/pen/packaging error/failure:	

Which of the following user errors apply? Tick all that apply:

__ Did not check expiration date

__ Did not check product solution

__ Incorrect choice of injection site

__ Needle cap not removed from syringe

__ Took longer than 5 minutes before carrying out the injection

__ Did not pinch the skin around the injection site

__ Did not insert the entire needle into the pinched area at an angle

__ Syringe pulled away before end of injection (i.e., before the plunger is pushed all the way down)

__ Did not move thumb up to allow the plunger to rise and activate the needle guard

__ Evidence of liquid leaking from injection site (i.e. potentially indicating a premature lift or a wet injection)

__ *Other* (*please specify below*).

Description of other user error:

Syringe failure. Tick all that apply:

__ Syringe leaking

__ Components broken / cracked

__ Liquid is cloudy, discoloured or contains large particles

__ Cannot remove needle cap

__ Bent needle

__ Cannot push the plunger rod down (i.e., required force is too high)

__ *Other* (*please specify below*)
Description of other syringe failure:
Packaging failure. Tick all that apply: __ Device damaged __ Packaging damaged or can't read label __ Security seal was broken __ Syringe missing from kit __ *Other* (*please specify below*)
Description of other packaging failure:

Error/failure outcome (check one):	**Resolution (check one) :**
☐ Subject received no dose ☐ Subject received a partial dose (*ensure date used is captured above)*	☐ Replacement syringe provided ☐ Dose omitted ☐ Subject withdrawn
Replacement Syringe Dispensed Date:	

Instructions for further processing: Please email completed Form to The GSK Safety Syringe Failure Processing Team at PPD Please contact your study monitor with any questions or for troubleshooting. Maintain the Form and in the subjects' records. You may be contacted further concerning the malfunctioned safety syringe.

12.13. Appendix 13 - Protocol Amendment Changes 02

Where this amendment Applies

This amendment applies across any site that will be used in the study.

Summary of Amendment Changes with Rationale

Minor changes overall to the document listing changes to abbreviations and text.

List of Specific Changes

Title: Cover page authors list

PREVIOUS TEXT

PPD

REVISED TEXT

Author (s): PPD

Title: Investigator Protocol Agreement page

PREVIOUS TEXT

For protocol number

REVISED TEXT

For protocol number **204958**

Title: Abbreviations updated for Subcutaneous in Overall Design page 10 and 17

PREVIOUS TEXT

All treatments will be administered **subcutaneous** by a health care professional (HCP). The study will compare the pharmacokinetics and safety of mepolizumab administered as a liquid drug product in two different devices with the reconstituted lyophilised drug product.

REVISED TEXT

All treatments will be administered **SC** by a health care professional (HCP). The study will compare the pharmacokinetics and safety of mepolizumab administered as a liquid drug product in two different devices with the reconstituted lyophilised drug product.

Title: Abbreviations updated for Confidence Interval in Analysis

PREVIOUS TEXT

Analysis

Point estimates and associated two-sided 90% confidence intervals will be constructed for the differences between the test and reference treatments on the $\log_e$ scale; these will be back-transformed to provide point estimates and two-sided 90% CIs for the ratio of each of the test treatments to the reference treatment on the original scale.

REVISED TEXT

Analysis

Point estimates and associated two-sided 90% confidence intervals **(CI)** will be constructed for the differences between the test and reference treatments on the $\log_e$ scale; these will be back-transformed to provide point estimates and two-sided 90% CIs for the ratio of each of the test treatments to the reference treatment on the original scale.

Title: Abbreviations updated for Confidence Interval in Analysis

PREVIOUS TEXT

Clinical data for mepolizumab administered by the **IV**, SC or IM routes in a variety of eosinophilic conditions is summarised in the Investigators' Brochure (GlaxoSmithKline Document Number CM 2003/00010/10).

REVISED TEXT

Clinical data for mepolizumab administered by the **intravenous (IV),** SC or IM routes in a variety of eosinophilic conditions is summarised in the Investigators' Brochure (GlaxoSmithKline Document Number CM 2003/00010/10).

Title: Updated text in Section 4.3 Type and Number of subjects

PREVIOUS TEXT

Additional subjects may be enrolled if deemed appropriate to ensure at least 216 completed subjects at the discretion of the Sponsor in consultation with the Investigator. (i.e. complete Day 85 visit). See Table 1

REVISED TEXT

Additional subjects may be enrolled if deemed appropriate to ensure at least 216 completed subjects at the discretion of the Sponsor in consultation with the Investigator. (i.e. complete Day 85 visit). See Table 1 **below.**

Title: Section 4.5 Dose Justification

PREVIOUS TEXT

A single mepolizumab dose of 100 mg administered **subcutaneous** is selected in this study as it is the approved therapeutic dose in severe asthma and the anticipated therapeutic dose in **COPD.**

REVISED TEXT

A single mepolizumab dose of 100 mg administered **SC** is selected in this study as it is the approved therapeutic dose in severe asthma and the anticipated therapeutic dose in **chronic obstructive pulmonary disease (COPD).**

Title: Section 4.6 Benefit:Risk Assessment

PREVIOUS TEXT

Summaries of findings from both clinical and non-clinical studies conducted with mepolizumab (SB-240563) lyophilised drug product can be found in the Investigator's Brochure.

REVISED TEXT

Summaries of findings from both clinical and non-clinical studies conducted with mepolizumab (SB-240563) lyophilised drug product can be found in the Investigator's Brochure **(IB).**

Title: Section 4.6.1 Risk Assessment – Text that has changed is included in the table below.

PREVIOUS TEXT

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Risk of Systemic Reactions, including allergic reactions	Biopharmaceutical products administered **subcutaneously** may elicit systemic (e.g. hypersensitivity) and local site reactions.	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of **adverse events**/SAE data from ongoing studies by the **GSK** study team and/or safety review team.
Injection site reactions		Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of **adverse events**/SAE data from ongoing studies by GSK study team and/or safety review team.

REVISED TEXT

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Risk of Systemic Reactions, including allergic reactions	Biopharmaceutical products administered **SC** may elicit systemic (e.g. hypersensitivity) and local site reactions.	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of **AE**/SAE data from ongoing studies by the **GlaxoSmithKline (GSK)**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		study team and/or safety review team.
Injection site reactions		Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of **AE**/SAE data from ongoing studies by GSK study team and/or safety review team.

Title: Section 6.2 Medical Devices

PREVIOUS TEXT

The instructions for use (IFU) of these injection devices are provided in the **study reference manual (SRM).** The instructions were developed and optimized as a result of formative human factors studies.

REVISED TEXT

The instructions for use (IFU) of these injection devices are provided in the **SRM**. The instructions were developed and optimized as a result of formative human factors studies.

Title: Section 6.6 Preparation/Handling/Storage/Accountability

PREVIOUS TEXT

A description of the methods and materials required for mepolizumab will be detailed in the Study Reference Manual (**SRM).**

REVISED TEXT

A description of the methods and materials required for mepolizumab will be detailed in the **SRM.**

Title: Section 6.11.1 Caffeine, Alcohol and Tobacco

PREVIOUS TEXT

- During the dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 12 hours prior to the start of dosing until collection of the final pharmacokinetic and/or **pharmacodynamic** sample of the session and prior to all out-patient visits.
- During the dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and/or **pharmacodynamic** sample of the session and prior to all out-patient visits.

REVISED TEXT

- During the dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 12 hours prior to the start of dosing until collection of the final pharmacokinetic and/or **PD** sample of the session and prior to all out-patient visits.
- During the dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and/or **PD** sample of the session and prior to all out-patient visits.

Title: Section 7. Study Assessments and procedures

PREVIOUS TEXT

- The timing and number of planned study assessments, including safety, pharmacokinetic, **pharmacodynamic**/biomarker 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.

REVISED TEXT

- The timing and number of planned study assessments, including safety, pharmacokinetic, **PD**/biomarker 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.

Title: 7.6.2 Sample Analysis

PREVIOUS TEXT

Plasma analysis will be performed under the control of PTS, **GlaxoSmithKline**, the details of which will be included in the Study Reference Manual (SRM).

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

REVISED TEXT

Plasma analysis will be performed under the control of PTS, **GSK,** the details of which will be included in the Study Reference Manual (SRM). Concentrations of mepolizumab 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 analyzed for mepolizumab any remaining plasma may be analyzed for other compound-related material and the results reported under a separate PTS, **GSK** protocol.

Title: Section 9.1 Hypotheses

PREVIOUS TEXT

For $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax, point estimates and corresponding two-sided 90% confidence intervals will be constructed for the ratio of the geometric mean of each test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference). No formal hypothesis will be tested. However, interpretation of the comparability of the autoinjector and safety syringe with the reconstituted lyophilised drug product will be guided by a two-sided 90% **confidence interval** for μ(test)/μ(reference) in the range (0.80, 1.25) for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax.

REVISED TEXT

For $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax, point estimates and corresponding two-sided 90% confidence intervals **(CI)** will be constructed for the ratio of the geometric mean of each test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference). No formal hypothesis will be tested. However, interpretation of the comparability of the autoinjector and safety syringe with the reconstituted lyophilised drug product will be guided by a two-sided 90% **CI** for μ(test)/μ(reference) in the range (0.80, 1.25) for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and Cmax.

Title: Section 9.2 Sample Size considerations

PREVIOUS TEXT

Variability estimates for $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$ and Cmax for mepolizumab were considered from three studies; SB-240563/017, SB-240563/018 and MEA114092. Only data from treatment groups with **subcutaneous** administration of mepolizumab in the upper arm, abdomen or thigh, for doses of 125mg and 250mg across the 3 studies was considered.

REVISED TEXT

Variability estimates for $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$ and Cmax for mepolizumab were considered from three studies; SB-240563/017, SB-240563/018 and MEA114092. Only data from treatment groups with **SC** administration of mepolizumab in the upper arm, abdomen or thigh, for doses of 125mg and 250mg across the 3 studies was considered.

Title: 9.5 Primary Analyses

PREVIOUS TEXT

Point estimates and associated two-sided 90% **confidence intervals** will be constructed for the differences between the test and reference treatments on the $\log_e$ scale; these will be back-transformed to provide point estimates and two-sided 90% CIs for the ratio of each of the test treatments to the reference treatment on the original scale.

REVISED TEXT

Point estimates and associated two-sided 90% **CI**s will be constructed for the differences between the test and reference treatments on the $\log_e$ scale; these will be back-transformed to provide point estimates and two-sided 90% CIs for the ratio of each of the test treatments to the reference treatment on the original scale.

Title: Section 11 References

PREVIOUS TEXT

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

REVISED TEXT

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

Title: Section: 12.1 Appendix 1 – Abbreviations and Trademarks

The following abbreviations and trademarks have been removed from this version of the protocol.

AD	**Atopic Dermatitis**
CPAP	**Continous Positive Airway Pressure**
LABA	**Long acting beta 2 agonist**
LTRA	**Leuketriene receptor anatagonist**

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ADVAIR™

Trademarks not owned by the GlaxoSmithKline group of companies
Chiron RIBA
SAS

12.14. Appendix 14 - Protocol Amendment Changes 03

Where this amendment Applies

This amendment applies across any site that will be used in the study.

Specific Change

Title: Section 7.3.1.4. Cardiovascular and Death Events

PREVIOUS TEXT

No cardiovascular or death events will be captured in this study as this is a healthy volunteer study.

REVISED TEXT

Section has been deleted from the document

Specific Change

Title: Section 7.3.1.4. Cardiovascular and Death Events

PREVIOUS TEXT

Section 7.3.1.4. Cardiovascular and Death Events

No cardiovascular or death events will be captured in this study as this is a healthy volunteer study.

REVISED TEXT

Upon deletion of Section 7.3.1.4 "Cardiovascular and Death Events" the subsequent Section 7.3.1.5 becomes 7.3.1.4, no change to body of text

Section 7.3.1.4. 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 subjects 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, Institutional Review Board (IRB)/Independent Ethics Committee (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.