TITLE PAGE

Protocol Title: A Phase 4, open-label, single arm, 24-week, study to evaluate the safety and efficacy of mepolizumab 100 mg SC administered every 4 weeks in Indian participants aged ≥18 years with Severe eosinophilic asthMa (PRISM)

Protocol Number: 209682 [Amendment 04]

Compound Number: SB240563

Study Phase: Phase 4

Short Title: Phase 4 study of mepolizumab 100 mg SC in Indian participants aged ≥18 years with severe eosinophilic asthma

Acronym: PRISM

Sponsor Name and Legal Registered Address:

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

Sponsor Contact Address

GlaxoSmithKline Pharmaceuticals Ltd.,
Dr. Annie Besant Road
Worli, Mumbai - 400030
Telephone: +91 22 24959595

Medical Monitor Name and Contact Information Will be provided separately

SPONSOR SIGNATORY

Dr. Robert Chan
Senior Clinical Development Director and Clinical
Development Leader Mepolizumab,
Clinical Sciences, GSK R&D

Approval Date: 23 Aug 2022

Sponsor Serious Adverse Events (SAE) Contact Information:

Email: india.pharmacovigilance@gsk.com
xPhone: +91-8657549542

Regulatory Agency Identifying Number(s): [Regulatory Agency identifying number(s) as appropriate]

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 4	*23 Aug 2022*	TMF-14888313
Amendment 3	*17-MAR-2021*	*TMF-11899446*
Amendment 2	*05-NOV-2020*	*2018N383582_01*
Amendment 1	*27-AUG-2019*	*2018N383582_00*
Original Protocol	*18-JAN-2019*	*2018N383582_00*

Amendment – 4

Overall Rationale for the Amendment:

Inclusion criteria no. 5 has been updated to align with the current management practice of SEA which does not include use of stable OCS use for prolonged periods of time and the changes are in line with Prescribing information of the product.

Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis, 2.1 Study Rationale, 2.3.1 Risk Assessment, 2.3.2 Benefit Assessment, 4. Study Design	The requirement of oral corticosteroids (OCS) and associated phases (Induction phase, optimization phase, OCS reduction/Maintenance phase) has been removed. CCI [redacted]	OCS requirement has been removed to align with the current management practice of SEA which does not include use of stable OCS use for prolonged periods of time and the changes are in line with prescribing information of the product.
1.2 Schema, 4.1 Overall Design	The schema has been updated with respect to the removal of OCS	Schema has been updated as OCS information is no longer required.
1.3 Schedule of Activities (SoA)	SoA has been updated for the removal of information regarding OCS and associated phases.	OCS requirement has been removed to align with the current management practice of SEA which does not include use of stable OCS use for prolonged periods of time and the changes are in line with prescribing information of the product .
	Stringency of spirometry timings (i.e. must be performed at the same time ±1 hour of the visit 1) has been removed.	To allow flexibility for the patients by broadening the time window for the spirometry within the day of the study visit.

Section # and Name	**Description of Change**	**Brief Rationale**
	Advisory statement for 12-Lead ECG has been added.	To maintain the uniformity across the protocol.
	Serum IgE (total) - Serum IgE has been removed from week 24 and IP discontinuation visit	Assessment of change from baseline is not an objective or endpoint of the study
3.0 Objectives and Endpoints	CCI [redacted]	Only a subset of patients (those completing or withdrawn from the study prior to protocol amendment 4) will be assessed for this endpoint where a structured OCS tapering schedule was mandated within the previous study protocols and protocol amendments
	Description of estimands have been added for all primary, secondary and exploratory endpoints	The rationale to add estimands is that estimands provide the precise description of what is being estimated for primary endpoints also explain about how to deal with intercurrent events which may occur during the study.
5 Study Population 6 Study Intervention 8 Efficacy Assessments	Inclusion criteria 5 has been updated with respect to the removal of requirement for background systemic corticosteroids. Information regarding OCS phases has also been removed. CCI [redacted]	OCS requirement has been removed to align with the current management practice of SEA which does not include the use of a stable OCS dose for prolonged periods of time and the changes are in line with prescribing information of the product. Only a subset of patients (those completing or withdrawn from the study prior to protocol amendment 4) will now be assessed for the CCI [redacted]
	Further additional details have been added regarding the efficacy endpoints.	Further additional clarifying text has been inserted regarding the efficacy endpoints to be studied under this protocol.
8.1.2 Number rate of clinically significant	Clinically significant exacerbations definition with	Additional clarifying text has been inserted regarding the definition of

Section # and Name	Description of Change	Brief Rationale
exacerbations	further clarifications added.	a clinically significant exacerbation for consistent reporting across all patients.
8.2.4 Electrocardiograms	The recommendation of triplicate 12-lead ECG within 4 minutes duration has been removed.	To reduce the burden to participants as a single twelve-lead ECG obtained at each timepoint specified in the Schedule of Activities (Section 1.3) is considered appropriate. Triplicate ECGs are required only if routine single ECG demonstrates a prolonged QT interval to obtain the averaged QTc in order to determine whether the patient should be discontinued from the study
9.1 Statistical Hypothesis	No hypothesis testing is to be performed for this study.	Sample size has been re-estimated based on probability of observing adverse events
9.2 Sample Size Determination	Sample size has been re-estimated based on primary endpoint and associated probabilities tables added.	The primary objective of study to evaluate the safety and tolerability of mepolizumab by descriptive statistics hence the sample size section has been updated to now be aligned with the primary objective.
9.3 Population for analyses	Enrolled Population definition has been updated and Per Protocol Population has been removed.	Enrolled Population definition is modified for summarizing reasons for screen and run-in failures. Inclusion criteria 5 is updated therefore no statistical analysis required of the Per Protocol Population.
9.4 Statistical Analyses 9.4.1 Safety Analyses	Further details on the reporting of the primary estimand have been inserted. CCI [redacted]	Further additional clarifying text has been inserted regarding the safety endpoints.

Section # and Name	Description of Change	Brief Rationale
	Subgroup analysis have been added using baseline OCS use (yes, no) for separate subgroup reporting.	Statistical and subgroup analysis has been updated for the separate reporting of subjects receiving baseline OCS use (yes, no).
9.4.2 Efficacy Analyses	CCI [redacted]. Further details on the estimation of secondary estimands has been added. Statistical analysis for secondary endpoints is updated with baseline OCS use (yes, no) included as a covariate within the analysis model.	CCI [redacted]. Further additional clarifying text has been inserted regarding the efficacy endpoints.
9.4.3 Health Outcomes Analyses	CCI [redacted].	Further additional clarifying text has been inserted regarding the reporting of the health outcomes endpoints.
10.3.5 Reporting of SAE to GSK	The information for reporting SAE to GSK has been updated.	To be consistent with the current mode of transmission of safety information as per agreed local practice.

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 4, open-label, single arm, 24-week, study to evaluate the safety and efficacy of Mepolizumab 100 mg SC administered every 4 weeks in Indian participants aged ≥18years with Severe eosinophilic asthma(PRISM).

Short Title: Phase 4 study of mepolizumab 100 mg SC in Indian participants aged ≥18 years with severe eosinophilic asthma

Rationale:

Indian Regulatory authorities have approved marketing of mepolizumab in India for the treatment of severe eosinophilic asthma based on data from multi-centre, multi-national studies. However, these studies did not include India as a participating country. As part of the approval process, the agency has asked for data to be generated in the Indian population.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety, and tolerability of mepolizumab in participants with severe refractory asthma with elevated eosinophils	The primary estimand will be defined by the following: Endpoints: • Incidence of on-treatment adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs) Summary measure: • Counts and percentages for incidence of at least one AE will be summarised overall, by system organ class and by preferred term Population of interest: • Severe refractory asthma patients in India with elevated eosinophils Key intercurrent events: • Discontinuation of treatment (for any reason) Strategy for intercurrent events: • While on-treatment strategy will be used for treatment discontinuation. This will estimate the percentage of participants experiencing an AE, while receiving treatment. AEs will be defined as on-treatment between the first dose up to and including 28 days following the last dose of mepolizumab. A supplementary estimand will be defined using

Objectives	Endpoints
	identical properties as for the primary estimand (summary measure, population of interest and key intercurrent events), however this supplementary estimand will report all AEs regardless of the discontinuation of study treatment. Endpoints: • Incidence of AEs and SAEs Strategy for intercurrent events: • Treatment policy strategy will be used for treatment discontinuation. This summary will therefore be inclusive of all on-treatment and post-treatment AEs.
Secondary	
• To evaluate the efficacy of mepolizumab in participants with severe refractory asthma with elevated eosinophils	The following secondary estimand is defined by the following: Endpoints: • Number of clinically significant exacerbations (including exacerbations requiring hospitalization or ED visits) • Number of exacerbations requiring hospitalization or ED visits • Number of exacerbations requiring hospitalization Summary measure: • Rate ratio comparing events/year during the 24-week follow-up period compared to the 12 months prior to screening Population of interest: • Severe refractory asthma patients in India with elevated eosinophils Key intercurrent events: • Discontinuation of treatment (for any reason) Strategy for intercurrent events: Treatment policy strategy will be used for treatment discontinuation. This will estimate the treatment effect over the 24 week study period regardless of treatment discontinuation. The remaining secondary estimands are defined by the following: Endpoints: • Change from baseline in clinic pre-bronchodilator FEV_1 at week 24 • Change from baseline in clinic post-bronchodilator FEV_1 at week 24 • Change from baseline in ACQ-5 score at week 24

Objectives	**Endpoints**
	• Change from baseline in morning PEF during weeks 20 - 24 Summary measure: • Mean change from baseline in clinic pre-bronchodilator FEV_1 at week 24 • Mean change from baseline in clinic post-bronchodilator FEV_1 at week 24 • Mean change from baseline in ACQ-5 score at week 24 • Mean change from baseline from baseline in morning PEF during weeks 20 – 24 Population of interest: • Severe refractory asthma patients in India with elevated eosinophils Key intercurrent events: • Discontinuation of treatment (for any reason) Strategy for intercurrent events: • Treatment policy strategy will be used for treatment discontinuation. This will estimate the treatment effect at the end of the 24 week study period regardless of treatment discontinuation
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Overall Design:

This is a multi-centre, open-label, single arm 24-week study.

During this study, all participants will remain on their existing maintenance asthma therapy throughout this study as per investigator's discretion, in addition to receiving mepolizumab 100 mg SC. OCS use and OCS dose adjustment in participants will be as per the investigator's discretion and clinical practice.

This is an Intervention Model single group study to evaluate the safety and efficacy of mepolizumab in participants with severe refractory asthma with elevated eosinophils.

Number of Participants:

Approximately 154 participants (Assuming 35% screen failure rate) will be required to be screened in order for 100 participants to be enrolled onto the study treatment.

Intervention Period and Duration:

Participants meeting all eligibility criteria at Visit 1 (Screening visit) will enter the study. The screening procedures will be performed -2 weeks to -1 week (screening visit would be at least 7 day prior to dosing visit) before first dose of mepolizumab. At Visit 2 (Week 0), participants will enter a 24-week treatment period, where mepolizumab 100 mg SC will be administered every 4 weeks. After the first dose of mepolizumab at Visit 2 (Week 0), participants will subsequently receive a further 5 doses of mepolizumab at 4 weekly intervals. Following the last dose of mepolizumab at Visit 7 (Week 20), the end of study Visit will occur 4 weeks later (Week 24).

Data Monitoring Committee: No

1.2. Schema

V1 V2* V3 V4 V5 V6 V7 V8

← -2 weeks → to -1 week ← Mepolizumab 100 mg, SC →

	W0	W4	W8	W12	W16	W20	W24
Screening visit (-2 weeks to -1 week)	Treatment Period						End of study visit

*All screening procedures will be performed at least -2 weeks to -1 week prior to first dose of mepolizumab at Visit 2 (Week 0). Screening visit would be at least 7 day prior to dosing visit.

V, visit; W, week; SC, subcutaneous

1.3. Schedule of Activities (SoA)

Table 1 Time and Events Table

Procedure	**Pre-Screen**	**Screening**	**Treatment Period (visit window is ± 7days)**						**IP Discontinuation visit**	**End of study visit**	**Notes**
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	
Week		**-2 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**4 weeks post last dose ± 7 days**	**24 or Early Withdrawal**	
Written Informed Consent	x	x									1. Pre-screen visit can occur on the same day as the Visit 1 but must be completed prior to starting Visit 1 (screening) procedures. 2. Visit 2 (Week 0) must occur at least one week following Visit 1 (screening) 3. Visit 2 (Week 0) will be considered Baseline
Demography		x									
Medical History		x									
Asthma and Exacerbation History (including triggers)		x									
Asthma Therapy History		x									Therapy history to include a detailed review of prior monoclonal antibodies received for treatment of asthma, including prior investigational anti-IL5 or anti-IL13 preparations.

Procedure	**Pre-Screen**	**Screening**	**Treatment Period (visit window is ± 7days)**						**IP Discontinuation visit**	**End of study visit**	**Notes**
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	
Week		**-2 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**4 weeks post last dose ± 7 days**	**24 or Early Withdrawal**	
Oral Corticosteroid Therapy History		x									
Smoking History		x									
Cardiovascular History/risk factors		x									
Parasitic Screening		x									
Inclusion/Exclusion Criteria		x	x								Study inclusion/exclusion criteria should be reviewed at the beginning of visit 2(Week 0). The review should include the results of any lab/safety assessments conducted at Visit 1 (screening).
Treatment Period Criteria			x								
Efficacy Assessments											
Exacerbation review			x	x	x	x	x	x	x	x	Number of clinically significant exacerbations (including exacerbations requiring hospitalization, Emergency Department) visits will be evaluated
Spirometry including FEV_1, FVC		x	x		x		x		x	x	

Procedure	**Pre-Screen**	**Screening**	**Treatment Period (visit window is ± 7days)**					**IP Discontinuation visit**	**End of study visit**	**Notes**
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	
Week		**-2 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**4 weeks post last dose ± 7 days**	**24 or Early Withdrawal**	
Maximum Post Bronchodilator Procedure		x	x						x	x	Maximum Post Bronchodilator Procedure is required to complete reversibility testing. If participant does not reverse ≥12% in FEV_1 at Visit 1 (screening), the procedure may be repeated at Visit 2 (Week 0).
OCS dose adjustment review (where applicable)		x		x	x	x	x	x			OCS dose adjustment should be reviewed at scheduled in-clinic Visits
ACQ-5 completion		x	x	x	x	x	x	x	x	x	The ACQ-5 should be completed weekly following Visit 1 (screening) through the participant's eDiary.
ACQ-5 review		x	x	x					x	x	
Review eDiary data (symptoms, PEF)			x	x	x	x	x	x	x	x	From Visit 1 (screening) to Visit 2 (Week 0) only, participants will record peak flow twice a day, subsequently on morning only eDiary data must be reviewed on every Visit
Health Outcome Assessments											
Clinician Rated Response to Therapy					x		x		x	x	
Participant Rated Response to Therapy					x		x		x	x	
WPAI-GH			x	x	x	x	x	x	x	x	

Procedure	**Pre-Screen**	**Screening**	**Treatment Period (visit window is ± 7days)**					**IP Discontinuation visit**	**End of study visit**	**Notes**
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	
Week		**-2 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**4 weeks post last dose ± 7 days**	**24 or Early Withdrawal**	
Safety Assessments											
Concomitant Medication		x	x	x	x	x	x	x	x	x	The concomitant procedures like Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 (screening) and throughout the study. Neither CPAP nor oxygen therapy may be initiated after Visit 1 (screening).
Physical Examination		x							x	x	
Detailed nasal exam (check for polyps)		x							x	x	
Vital Signs		x	x	x	x	x	x	x	x	x	1. Vital signs to be taken before blood collection for laboratory tests. 2. Vital signs will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.
12 lead ECG		x	x		x		x		x	x	12-lead ECG should be obtained after the patient has been rested in a supine position for at least 5 minutes.
Adverse Events		x	x	x	x	x	x	x	x	x	
Serious Adverse Events		x	x	x	x	x	x	x	x	x	

Procedure	**Pre-Screen**	**Screening**	**Treatment Period (visit window is ± 7days)**						**IP Discontinuation visit**	**End of study visit**	**Notes**
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	
Week		**-2 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**4 weeks post last dose ± 7 days**	**24 or Early Withdrawal**	
Steroid withdrawal exam review (where applicable)		x	x	x	x	x	x	x	x	x	
Laboratory Assessments											During the treatment period, all lab samples should be obtained **pre-dose**
Haematology with differential		x	x	x	x	x	x	x	x	x	
Chemistry		x	x	x	x	x	x	x	x	x	
Urinalysis		x									
Pregnancy test		S	U	U	U	U	U	U	U	U	Pregnancy test; S = serum, U= urine
HBsAg and hepatitis C antibody		x									Hepatitis B Antigen and Hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RIBA immunoblot assay should be reflexively performed on the serum sample to confirm the result)
Serum IgE (total)	x	x	x								Serum IgE (Total) can be evaluated either at Pre-Screen visit i.e. before screening of patients (prior to Visit 1) or on the same day as ScreeningVisit 1.

Procedure	**Pre-Screen**	**Screening**	**Treatment Period (visit window is ± 7days)**						**IP Discontinuation visit**	**End of study visit**	**Notes**
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	
Week		**-2 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**4 weeks post last dose ± 7 days**	**24 or Early Withdrawal**	
Immunogenicity Assessments			x						x	x	Serum sample will be collected at end of study visit OR at IP discontinuation visit. Sample collection to happen at 4 weeks from last dose of mepolizumab or at patient's last visit in case patient discontinues from the study
Investigational Product (IP)											
Administer IP			x	x	x	x	x	x			
Oral Corticosteroids dispensed (as needed)		x	x	x	x	x	x	x			
Salbutamol dispensed (as needed)		x	x	x	x	x	x	x			
Collect dispensed salbutamol as needed			x	x	x	x	x	x	x	x	
eCRF											
Complete eCRF		x	x	x	x	x	x	x	x	x	
Dispense paper worksheets		x	x	x	x	x	x	x	x		
Dispense eDiary and PEF meter		x									
Collect eDiary and PEF meter										x	
Collect/review paper worksheets			x	x	x	x	x	x	x	x	

2. INTRODUCTION

Mepolizumab is a humanized monoclonal antibody (IgG1, kappa) that blocks interleukin-5 (IL-5) from binding to the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits signalling, resulting in the reduction in production and survival of eosinophils. Mepolizumab is licensed for add-on maintenance treatment for severe eosinophilic asthma at a dose of 100 mg every 4 weeks and is available as a powder for solution for subcutaneous (SC) injection.

2.1. Study Rationale

This phase 4 study is a post-approval commitment for Marketing Authorization granted by the Drugs Controller General of India (Indian Regulatory Agency).

In this phase 4 study, we will evaluate effect of mepolizumab as an adjunctive subcutaneous therapy in Indian patients 18 years and above age with severe eosinophilic asthma.

2.2. Background

Asthma is a common chronic inflammatory disease of the airways that affects 5 to 10% of adults and children (Bateman, 2004). The prevalence of asthma in India is about 2% with a burden of about 17 million asthmatic patients (Agarwal, 2015). The majority of patients with asthma can be adequately controlled by following step-wise treatment recommendations (GINA, 2015; NIH, 2007). However, a small minority of patients experience uncontrolled asthma despite following step-wise treatment recommendations (e.g., high dose ICS plus additional controller medications). Although patients with uncontrolled severe asthma represent less than 5% of the total asthma population (Barnes, 1996), these patients experience considerable morbidity (Polosa, 2008) and are responsible for approximately 50% of total health care costs associated with asthma (Cisternas, 2003). Studies in the severe asthma population have shown that more than half of these patients have persistent eosinophilic (>300 cells/microL) airway inflammation despite corticosteroid therapy (Wenzel, 2005).

The American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force (Chung, 2014) for severe asthma recommends that control should first be attempted through the use of high-dose ICS before adding daily OCS or omalizumab (for the subgroup of patients with elevated IgE and who are allergic to a perennial allergen). Patients with severe asthma have complex treatment requirements, which in 30 to 40% of such patients include the regular use of oral glucocorticoids to control their asthma. Use of OCS on a regular basis have well-documented side effects also adherence to daily OCS has been documented to be as low as 50% (Robinson, 2003; Gamble, 2009). Such therapy can result in serious and often irreversible adverse effects. Current treatments with glucocorticoid-sparing properties are not recommended in patients with severe asthma because of their high risk–benefit ratio. Due to the undesirable safety profile of OCS and the limited application of omalizumab in severe asthma (Normansell, 2014), there are few treatment options to reduce the frequency of exacerbations and the dependence on systemic corticosteroids for patients with severe eosinophilic asthma.

Thus, there remains a high unmet need to provide better treatment options, without the side effects associated with systemic corticosteroids, for this small segment of the asthma population.

Mepolizumab binds with high specificity and affinity to human interleukin 5 (IL-5), the key cytokine responsible for regulation of blood and tissue eosinophils. The overproduction of IL-5 has been specifically reported in patients with a variety of eosinophil associated disorders including asthma (Robinson, 1992; Sur, 1995). By targeting IL-5, mepolizumab prevents IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits IL-5 signalling and the overexpression of peripheral blood and tissue eosinophils. Eosinophilic inflammation of the airways plays a central role in the pathogenesis of asthma (Seminario, 1994; Rothenberg, 1998; Wardlaw, 2000; Cohn, 2004). Available data do not indicate that reduction of eosinophils has any untoward effects on normal health (Gleich, 2013); patients lacking eosinophils in association with immunodeficiency or as a consequence of IgG-mediated eosinophil precursor destruction do not display any distinguishing abnormalities related to the eosinophil reduction. Thus, a therapeutic strategy targeting IL-5 with mepolizumab represents a focused therapeutic option, which results in reduced eosinophil levels and important clinical benefits for patients with eosinophilic inflammation associated with severe asthma who are receiving optimised standard of care therapy (Haldar, 2011; Pavord, 2012).

The drug is indicated as an add-on treatment for severe eosinophilic asthma, on the basis of its clinical benefit in this setting in the placebo-controlled DREAM, MENSA and SIRIUS trials. Based on the 52-week, phase II, DREAM study (which assessed varying intravenous mepolizumab dosages), intravenous mepolizumab 75 mg every 4 weeks (q4w) and the corresponding (recommended) subcutaneous dosage of 100 mg q4w were studied in the 32- and 24-week phase III MENSA and SIRIUS trials. In patients aged >12 years with severe eosinophilic asthma in the phase III studies, adding subcutaneous mepolizumab 100 mg q4w to current asthma therapy significantly reduced the rate of clinically relevant asthma exacerbations. This mepolizumab regimen also significantly improved asthma control, health-related quality of life and (in one of the two studies) lung function and had acceptable tolerability (with headache the most common adverse event). In the MENSA and SIRIUS extension, COSMOS, mepolizumab provided durable clinical benefit over up to 84 weeks' therapy with no new tolerability concerns. COLUMBA study reported long-term safety data for mepolizumab in patients with severe eosinophilic asthma with exposure for up to 4.5 years. There was no evidence that long term exposure to mepolizumab altered the safety or tolerability profile. Rates of AEs and SAEs reported in this study are in line with those reported in previous mepolizumab randomized controlled trials (Ortega, 2018). In COSMEX study it was found that the safety profile of mepolizumab was similar to previous shorter-term trials, with no new safety signals; long-term treatment provided sustained & consistent exacerbation & OCS reductions for up to 4.5yrs (Albers, 2018). Thus, mepolizumab is a valuable add-on treatment option for adults and adolescents aged 12 years or above who have severe eosinophilic asthma despite optimized standard therapies. Mepolizumab, based on its favourable safety profile, the robust data supporting its effectiveness in reducing frequent and severe exacerbations, improvements in quality of life, and in reducing the requirement for daily systemic corticosteroids with established long-term safety for

periods up-to 4.5 years provides a treatment option for patients who otherwise have no, or limited therapeutic treatment options (Deeks, 2016).

A proof-of-concept study involving 20 patients with eosinophilic asthma showed that the intravenous administration of mepolizumab was effective in reducing the maintenance dose of prednisone while preventing exacerbations (Nair, 2009). In the Steroid Reduction with Mepolizumab Study (SIRIUS), the effect of mepolizumab adjunctive subcutaneous therapy was compared with that of placebo in reducing the use of maintenance oral glucocorticoids while maintaining asthma control in patients with severe eosinophilic asthma. In patients requiring daily oral glucocorticoid therapy to maintain asthma control, mepolizumab had a significant glucocorticoid-sparing effect, reduced exacerbations, and improved control of asthma symptoms (Bel, 2014).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of mepolizumab may be found in the Investigator's Brochure, Participant Information Leaflet, Prescribing Information.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) (mepolizumab)		
Systemic Reactions (Allergic [type I hypersensitivity] and Other systemic reactions) including Anaphylaxis	There have been reports of systemic reactions (including hypersensitivity reactions, such as anaphylaxis, bronchospasm, angioedema, rash, urticaria and hypotension) with mepolizumab. These are usually acute, occurring within a few hours of the drug being administered, but can also be delayed, occurring after several days	Safety monitoring of participants will occur during SC administration and for one hour after the end of injection for the first 3 injections, then per institutional guidelines. Such monitoring will include general safety monitoring including monitoring for both systemic reactions (Allergic [type I hypersensitivity] and Other systemic reactions) and local site reactions. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there must be personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the patient including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate. Customised AE and SAE case report form (CRF) utilised for targeted collection of information for systemic reaction adverse events. Use of Joint National Institute of Allergy and Infectious Diseases (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 7).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
There are few invasive procedures such as blood collection for chemistry assessment in which blood will be collected from peripheral veins. Also, ECG assessment will be conducted.	Fainting associated with needle prick and contact dermatitis because of jelly applied before ECG assessment	The participants have been informed about the all the study procedures and invasive procedure for e.g. blood collection during informed consent process. No further risk mitigation strategy is required.
COVID-19 pandemic		
COVID-19 pandemic	The COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures.	Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation. Visits that were conducted via the telephone will not be classified as missed visits, however missed assessments (e.g. spirometry) should be recorded as COVID-19 protocol deviations. The study CRF will capture information on probable, suspected or confirmed COVID-19 infections. Additionally, a further targeted CRF page will capture the frequency of missed or partially completed study visits or assessments due to the COVID-19 pandemic. Home healthcare visits (home visits and telemedicine visits) may be implemented for scheduled visits from Visit 3 onwards for participants unable to attend a site visit due to COVID-19 related restrictions. Intercurrent events related to the COVID-19 pandemic (such as quarantines, site closures or other related issues) will be accounted for

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		within the analysis of the study.

2.3.2. Benefit Assessment

During the entire duration of the study, all the participants will receive medicines such as mepolizumab, OCS (as needed) and ICS plus LABA combination free of cost. Also, all the routine procedures, which are offered as standard of care for Asthma evaluation (for e.g. Spirometry assessment) and safety assessment (ECG, chemistry) will be provided free of cost.

Multiple clinical studies (MENSA, SIRIUS, COSMOS) have shown that mepolizumab has significantly reduced clinically significant annual asthma exacerbation rate and improved lung function in patients with severe eosinophilic asthma. SIRIUS study demonstrated that in patients requiring daily oral glucocorticoid therapy to maintain asthma control, mepolizumab had a significant glucocorticoid-sparing effect.

2.3.3. Overall Benefit: Risk Conclusion

The benefit: risk of mepolizumab 100mg SC every 4 weeks in the approved indication of severe eosinophilic asthma is positive.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety, and tolerability of mepolizumab in participants with severe refractory asthma with elevated eosinophils	The primary estimand will be defined by the following: <u>Endpoints:</u> • Incidence of on-treatment adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs) <u>Summary measure:</u> • Counts and percentages for incidence of at least one AE will be summarised overall, by system organ class and by preferred term <u>Population of interest:</u> • Severe refractory asthma patients in India with elevated eosinophils <u>Key intercurrent events:</u> • Discontinuation of treatment (for any reason) <u>Strategy for intercurrent events:</u> • While on-treatment strategy will be used for treatment discontinuation. This will estimate the percentage of participants experiencing an AE, while receiving treatment. AEs will be defined as on-treatment between the first dose up to and including 28 days following the last dose of mepolizumab. A supplementary estimand will be defined using identical properties as for the primary estimand (summary measure, population of interest and key intercurrent events), however this supplementary estimand will report all AEs regardless of the discontinuation of study treatment. <u>Endpoints:</u> • Incidence of AEs and SAEs <u>Strategy for intercurrent events:</u> • Treatment policy strategy will be used for treatment discontinuation. This summary will therefore be inclusive of all on-treatment and post-treatment AEs.
Secondary	
• To evaluate the efficacy of mepolizumab in participants	The following secondary estimand is defined by the following:

Objectives	**Endpoints**
with severe refractory asthma with elevated eosinophils	Endpoints: • Number of clinically significant exacerbations (including exacerbations requiring hospitalization or ED visits) • Number of exacerbations requiring hospitalization or ED visits • Number of exacerbations requiring hospitalization Summary measure: • Rate ratio comparing events/year during the 24-week follow-up period compared to the 12 months prior to screening Population of interest: • Severe refractory asthma patients in India with elevated eosinophils Key intercurrent events: • Discontinuation of treatment (for any reason) Strategy for intercurrent events: • Treatment policy strategy will be used for treatment discontinuation. This will estimate the treatment effect over the 24 week study period regardless of treatment discontinuation. The remaining secondary estimands are defined by the following: Endpoints: • Change from baseline in clinic pre-bronchodilator FEV_1 at week 24 • Change from baseline in clinic post-bronchodilator FEV_1 at week 24 • Change from baseline in ACQ-5 score at week 24 • Change from baseline in morning PEF during weeks 20 - 24 Summary measure: • Mean change from baseline in clinic pre-bronchodilator FEV_1 at week 24 • Mean change from baseline in clinic post-bronchodilator FEV_1 at week 24 • Mean change from baseline in ACQ-5 score at week 24 • Mean change from baseline from baseline in morning PEF during weeks 20 – 24 Population of interest: • Severe refractory asthma patients in India with elevated eosinophils Key intercurrent events: • Discontinuation of treatment (for any reason)

Objectives	**Endpoints**
	<u>Strategy for intercurrent events:</u> • Treatment policy strategy will be used for treatment discontinuation. This will estimate the treatment effect at the end of the 24 week study period regardless of treatment discontinuation.
Exploratory	
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a multi-centre, open-label, single arm 24-week study.

V1 V2* V3 V4 V5 V6 V7 V8

← -2 weeks to -1 week → ← Mepolizumab 100 mg, SC →

	W0	W4	W8	W12	W16	W20	W24
Screening visit (-2 weeks to -1 week)	Treatment Period						End of study visit

*All screening procedures will be performed at least -2 weeks to -1 week prior to first dose of mepolizumab at Visit 2 (Week 0). Screening visit would be at least 7 day prior to dosing visit.

V, visit; W, week; SC, subcutaneous

The primary estimand is the incidence of AEs, SAEs and AESIs in adult Indian participants with severe refractory asthma with elevated eosinophils while on-treatment with mepolizumab 100mg SC during a 24-week study.

4.1.1. Screening

Participants who meet all eligibility criteria at the Screening visit (Visit 1) will enter the study and asked to come to the clinic after at least 1 week for Visit 2 (Week 0).

Participants must understand and agree to use the study drugs for the treatment of asthma, or asthma exacerbation, for the duration of the study. OCS use and OCS dose adjustment in participants will be as per the investigator's discretion and clinical practice.

At Visit 1, the screening visit, the screening ACQ-5 score will be captured. Participants who meet study eligibility criteria, are eligible to enter the Treatment period. All screening procedures will be performed -2 weeks to -1 week (screening visit would be at least 7 day prior to dosing visit) before first dose of mepolizumab (Visit 2, Week 0).

The ACQ-5 questionnaire has been validated in several separate studies and the minimal clinically important difference value of +0.5 has been established to demonstrate a significant clinical change in asthma status (Juniper, 1999; Korn, 2011).

4.1.1.1. Exacerbation Management

Anytime during the study when a participant experiences an exacerbation the exacerbation should be treated according to the investigator's clinical practice.

4.1.2. Treatment period

At Visit 2 (Week 0), participants who meet the Treatment Period eligibility criteria will receive Mepolizumab 100mg SC every 4 weeks.

Subsequently, participants will continue to receive with mepolizumab 100mg SC every 4 weeks. During this period, participants will remain on their baseline asthma medications. OCS use and OCS dose adjustment in participants will be as per the investigator's discretion and clinical practice.

4.1.2.1. Exacerbation Management during Treatment Period

Anytime during the study when a participant experiences an exacerbation the exacerbation should be treated according to the investigator's clinical practice.

The participant will return for each subsequent Visit, to receive their subsequent doses of open label study treatment, as scheduled.

4.1.3. IP Discontinuation Visit

The IP discontinuation visit will be performed 4 weeks following the last dose of mepolizumab with a window of ±7 days. Also, if a participant permanently stops study intervention, the participant is not required to withdraw from the study. Every effort should be made by the PI/staff to keep the subject in the study to collect important efficacy and safety data. In the event of discontinuation of study, the end of study visit activities should be performed as specified in SoA table (Section 1.3).

4.2. Scientific Rationale for Study Design

Though safety and efficacy of mepolizumab in patients with severe eosinophilic asthma has been established in various clinical studies across USA and Europe, this will be the first clinical study to assess safety in Indian patients.

Eosinophilic inflammation of the airways plays a central role in the pathogenesis of asthma (Seminario, 1994; Rothenberg, 1998; Wardlaw, 2000; Cohn, 2004). The overproduction of IL-5 has been specifically reported in patients with a variety of eosinophil associated disorders including asthma (Robinson, 1992; Sur, 1995). Mepolizumab binds with high specificity and affinity to human interleukin 5 (IL-5), the key cytokine responsible for regulation of blood and tissue eosinophils. A therapeutic strategy targeting IL-5 with mepolizumab represents a focused therapeutic option, which results in reduced eosinophil levels and important clinical benefits for patients with eosinophilic inflammation associated with severe asthma who are receiving optimised standard of care therapy.

There is significant unmet medical need to provide better treatment options in patients with severe eosinophilic asthma who need systemic corticosteroids for maintenance, given undesirable safety profile of OCS and the limited application of omalizumab in severe asthma (Normansell, 2014). In patients aged ≥12 years with severe eosinophilic asthma in the phase III studies, adding subcutaneous mepolizumab 100 mg q4w to current asthma therapy significantly reduced the rate of clinically relevant asthma exacerbations and significantly improved asthma control and had acceptable tolerability (with headache the most common adverse event). Further, the SIRIUS study demonstrated that in patients requiring daily oral glucocorticoid therapy to maintain asthma control, mepolizumab had a significant glucocorticoid-sparing effect. This study will also evaluate the OCS sparing effect in Indian patients with severe eosinophilic asthma (only to be assessed in patients who completed or withdrew from the study prior to the adoption of protocol amendment 4).

4.3. Justification for Dose

Mepolizumab 100 mg SC every 4 weeks is as per approved dose (Prescribing Information) by Indian Regulatory Authorities.

4.4. End of Study Visit

A participant is considered to have completed study treatment if he/she has received a dose of mepolizumab at Visit 7 (Week 20) of the study.

A participant is considered to have completed the study if he/she has completed the 24 week treatment period of the study including the end of study visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participant must be ≥18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Asthma: Evidence of asthma as documented by either:
   - Airway reversibility (FEV1≥12% and 200 ml) demonstrated at Visit 1 (screening), or Visit 2 (Week 0) OR documented in the previous 12 months OR
   - Airway hyper-responsiveness (methacholine: PC20 of <8mg/mL or histamine: PD20 of <7.8 µmol; mannitol: decrease in FEV1 as per the labelled product instructions) documented in the 12 months prior to Visit 2 (Week 0) OR
   - Airflow variability in clinic FEV1 ≥20% between two consecutive clinic visits documented in the 12 months prior to Visit 2 (FEV1 recorded during an exacerbation should not be considered for this criteria) OR
   - Airflow variability as indicated by >20% diurnal variability in peak flow observed on 3 or more days during the optimisation period
3. Participants with Eosinophilic asthma: prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma as

   FEV1: Persistent airflow obstruction as indicated by:

   For participants ≥ 18 years of age at Visit 1 (screening), or Visit 2 (Week 0), a pre-bronchodilator FEV1 <80% predicted

   For predicted FEV1 values NHANES III values will be used and adjustments to these values will be made for race [Hankinson, 1999].
4. Eosinophilic Phenotype: Airway inflammation characterized as eosinophilic in nature as indicated by one of the following characteristics:

   a. An elevated peripheral blood eosinophil level of ≥300 cells/µL that is related to asthma within the previous 12 months prior to Visit 2 (Week 0)

   OR

   b. Peripheral baseline eosinophil level ≥150 cells/µL between Visit 1 (screening) and Visit 2 (Week 0) that is related to asthma

5. Patients eligible for mepolizumab treatment as per independent clinical judgment of treating physician in alignment with local prescribing information.
6. Inhaled Corticosteroids: requirement for regular treatment with high dose inhaled corticosteroid in the 6 months prior to Visit 1 (screening).

   For 18 years of age and older:

   - ICS dose must be ≥880 mcg/day fluticasone propionate (FP) (ex-actuator) or equivalent daily.
7. Controller Medication: Current treatment with an additional controller medication for at least 3 months OR having used and failed an additional controller medication for at least 3 successive months during the prior 12 months [e.g., long-acting beta2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline].

Sex

8. Male or eligible female

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

Female Participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)

  OR

- Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 during the intervention period and for at least 16 weeks after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive (Appendix 2) pregnancy test (serum) within 8 weeks before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. Concurrent Respiratory Disease: Presence of a clinically important lung condition other than asthma. This includes but is not limited to current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer.
2. Malignancy: A current malignancy or previous history of cancer in remission for less than 12 months prior screening (Participants who had localized carcinoma (i.e. basal or squamous cell) of the skin which was resected for cure will not be excluded).
3. Liver Disease: Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices or persistent jaundice), cirrhosis, and known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. Cardiovascular: Participants who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment. Including but not limited to:
   - known ejection fraction of <30% OR
   - severe heart failure meeting New York Heart Association Class IV (Appendix 5) OR
   - hospitalised in the 12 months prior to Visit 1 (screening) for severe heart failure meeting New York Heart Association Class III (Appendix 5) OR
   - angina diagnosed less than 3 months prior to Visit 1 (screening) or at Visit 1
5. Other Concurrent Medical Conditions: Participants who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.
6. Eosinophilic Diseases: Participants with other conditions that could lead to elevated eosinophils such as Hypereosinophilic Syndromes, including Churg-Strauss Syndrome, or Eosinophilic Esophaghitis.
7. Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 (screening) are also to be excluded.

Prior/Concomitant Therapy

8. Omalizumab Use: Participants who have received omalizumab [Xolair] within 130 days of Visit 1 (screening)
9. Other Monoclonal Antibodies: Participants who have received any monoclonal antibody (other than Xolair) to treat inflammatory disease within 5 half-lives of Visit 1 (screening)

10. Investigational Medications: Participants who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to Visit 1 (this also includes investigational formulations of marketed products).

Prior/Concurrent Clinical Study Experience

11. Participants who have previously participated in any study of mepolizumab and received Investigational Product (including placebo).

Diagnostic assessments

12. ECG: ECG assessment QTcF > 450msec or QTcF > 480 msec for participants with Bundle Branch Block.

    Participants are excluded if an abnormal ECG finding from the 12-lead ECG conducted at Screening (Visit 1) is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator.

13. Immunodeficiency: A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of corticosteroids taken as therapy for asthma

COVID-19 Related Exclusion

14. Participants that have a current active COVID-19 infection, either laboratory confirmed or according to the investigator's medical judgement.

    Note: Participants who have confirmed or suspected COVID-19 infection may be re-screened 4 weeks or more after the resolution of the COVID-19 infection and only after written approval from the study Medical Monitor.

15. Participants known to be in contact with active COVID-19 positive individuals within the past 14 days.

    Note: Participants may be re-screened 14 days or more following the contact, during which the participant should remain symptom free, and only after written approval from the study Medical Monitor.

Other Exclusions

16. Smoking history: Current smokers or former smokers with a smoking history of ≥10 pack years. A former smoker is defined as a participant who quit smoking at least 6 months prior to Visit 1 (screening)
17. Hypersensitivity: Participants with a known allergy or intolerance to a monoclonal antibody or biologic.
18. Pregnancy: Participants who are pregnant or breastfeeding. Patients should not be enrolled if they plan to become pregnant during the time of study participation.

19. Alcohol/Substance Abuse: A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1 (screening).
20. Adherence: Participants who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.

Re-screening of participants will be allowed only upon approval by the medical monitor.

5.3. Treatment Period Criteria

Study participants must fulfil the following criteria in order to enter the Treatment Period (recruitment continues until approximately 100 participants enter Treatment Period):

1. Eosinophilic asthma: Prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma as per Inclusion Criteria 3 and 4

2. eDiary Compliance: Compliance with completion of the eDiary defined as:

   - Completion of symptom scores on 4 or more days out of the last 7 days immediately preceding Visit 2 (Week 0)

   - Completion of information relating to rescue medication use on 4 or more days out of the last 7 days immediately preceding Visit 2 (Week 0).

   - Completion of PEF measurements on 4 or more days out of the last 7 days immediately preceding Visit 2 (Week 0).

3. Laboratory abnormality: No evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1 (screening), as judged by the investigator.

4. Alanine transferase (ALT) < 2 x upper limit of normal (ULN)

5. Bilirubin < 1.5 x ULN (isolated bilirubin >1.5 ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

6. No cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, or persistent jaundice. Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C e.g., presence of hepatitis B surface antigen [HBsAg] or positive hepatitis C antibody test result) is acceptable if the participant otherwise meets eligibility criteria

5.4. Lifestyle Considerations

5.4.1. Caffeine, Alcohol, and Tobacco

- Participants who use tobacco products will be instructed that use of tobacco products will not be allowed from screening until after the end of study visit.

5.5. Screen Failures

Participants will be assigned a study number at the time of signing the consent. Participants who do not progress to the screening visit (Visit 1) will be deemed a Pre-screen Failure. No data will be captured in the eCRF for these participants.

Those participants that complete at least one additional procedure at Visit 1 (screening) but do not enter the Screening Period (between Visit 1 and Visit 2) will be designated as screen failures. Additionally, those participants that enter the Screening Period, but do not complete any Visit 2 procedures will be designated as run-in failures.

A minimal set of screening information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Re-screening of participants will be allowed only upon approval by the medical monitor. If a patient is approved to be re-screened the patient would be required to repeat the screening process again from the start of the time and events table, including screening visit and would be assigned a new subject number.

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

Arm Name	Single arm study
Intervention Name	Mepolizumab
Type	Biologic
Dose Formulation	Vial
Unit Dose Strength(s)	100 mg/ml
Dosage Level(s)	100 mg every 4 weeks
Route of Administration	Subcutaneous
IMP and NIMP	
Sourcing	Provided centrally by the Sponsor

Packaging and Labelling	Study Intervention will be provided in vial. Each vial will be labelled as required per country requirement.
Current Name	Nucala

6.2. Preparation/Handling/Storage/Accountability

1. Mepolizumab will be provided as a lyophilised powder in sterile vials for individual use. The vial will be reconstituted with Sterile Water for Injection, just prior to use. To administer mepolizumab 100 mg SC, reconstituted mepolizumab for injection will be drawn into a 1.0 ml polypropylene syringe. Study staff member will administer the SC dose into the participant's upper arm, thigh or abdomen. Further details of dose preparation and administration can be found in the Clinical Investigator's Brochure (CIB) [GlaxoSmithKline Document Number CM2003/00010/07], and the Study Reference Manual (SRM)
2. Safety monitoring of participants will occur during SC administration and for one hour after the end of injection for the first 3 injections, then per institutional guidelines. Such monitoring will include general safety monitoring including monitoring for both systemic hypersensitivity (i.e., allergic/IgE-mediated and non-allergic) and local site reactions. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there must be personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the patient including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.
3. Under normal conditions of handling and administration, study intervention 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. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
4. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.
5. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
6. Only participants who enter the Treatment Period may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. Mepolizumab must be stored under the appropriate physical conditions which includes storage in a

refrigerator or at a temperature of 2-8°C and protected from light. The contents of the label will be in accordance with all applicable regulatory requirements.

7. The investigator/ designee, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Product accountability records must be maintained throughout the course of the study.
8. Further guidance and information for the final disposition of unused study intervention are provided in the SRM Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is single arm, open label study. Therefore, randomization and blinding are not applicable.

6.4. Study Intervention Compliance

- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.
- When participants self-administer asthma medications (other than mepolizumab), compliance with orally administered drugs for asthma (leukotriene receptor antagonists etc) will be assessed through querying the participant during the site visits and documented in the source documents and CRF. A record of the number of tablets dispensed to and taken by each participant for asthma management must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5. Concomitant Therapy

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

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

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

6.5.1. Rescue Medicine

The study site will supply Salbutamol metered dose inhaler rescue medication that will be provided by the sponsor.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.5.2. Permitted Medications and Non-Drug Therapies

OCS use is permitted as per investigator's discretion and changes must be recorded accurately in the eCRF.Additional asthma medications such as theophylline or anti-leukotrienes will be permitted provided they have been taken regularly in the 3 months prior to entering the Treatment Period (Visit 2, Week 0).

Continuous Positive Airway Pressure (CPAP) for the treatment of obstructive sleep apnoea is permitted, if initiated prior to the screening visit. This treatment must be captured in the eCRF.

6.5.3. Prohibited Medications and Non-Drug Therapies

During this study the OCS may be used for the treatment of asthma, as needed by the investigator.

Prior to screening the following medications are prohibited for the timeframe indicated in Table 2. These medications are also prohibited throughout the study.

Table 2 Medications not allowed prior to the screening visit and throughout the study

Medication	**Washout Time Prior to Screening Visit**
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab [Xolair]	130 days
Other monoclonal antibodies	5 half-lives
Experimental anti-inflammatory drugs (non-biologicals)	3 months
Immunosuppressive medications such as those listed below (not all inclusive)	
Corticosteroids intramuscular, long-acting depot if used to treat a condition other than asthma	3 months
Methotrexate, troleandomycin, cyclosporin, azathioprine	1 month
Oral gold	3 months
Chemotherapy used for conditions other than asthma	12 months
Regular systemic (oral or parenteral) corticosteroids for the treatment of conditions other than asthma	3 months

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 (screening) and throughout the study. Neither CPAP nor oxygen therapy may be initiated after Visit 1 (screening).

6.6. Dose Modification

Dose of mepolizumab will remain constant throughout the study.

6.7. Intervention after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition. GSK will not supply mepolizumab post study since the mepolizumab will be available commercially. At the end of the study, participants may be prescribed appropriate alternative asthma therapy if needed and as determined by the study Investigator.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants who permanently stop study intervention are not required to withdraw from the study. If for any reason a participant must permanently stop study intervention every effort should be made by the PI/staff to keep the subject in the study to collect important efficacy and safety data.
See the SOA for data to be collected at the time of discontinuation of study intervention.

7.1.1. Liver Chemistry Stopping Criteria

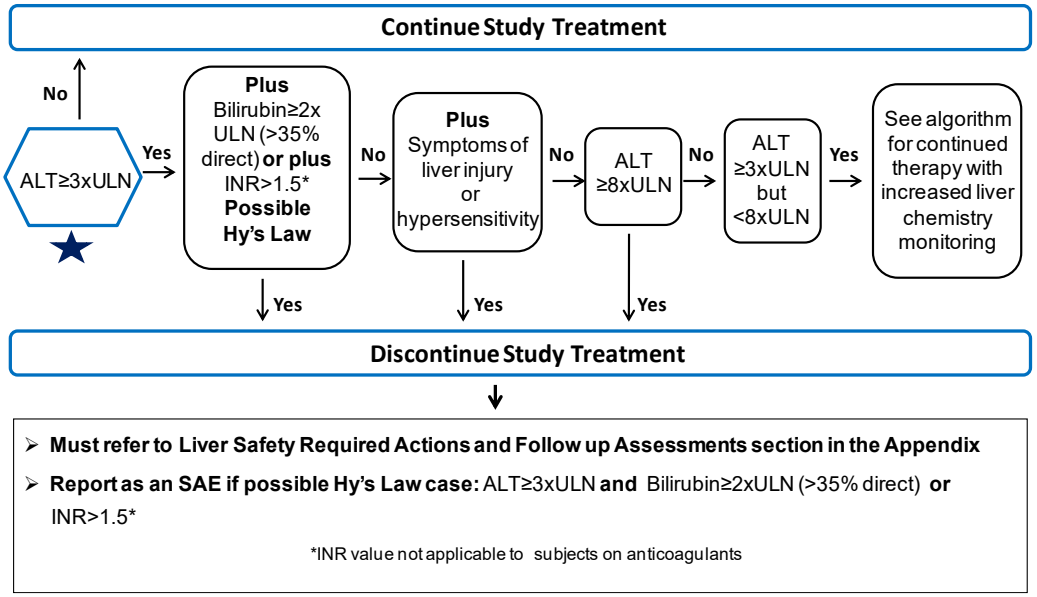
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm OR
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

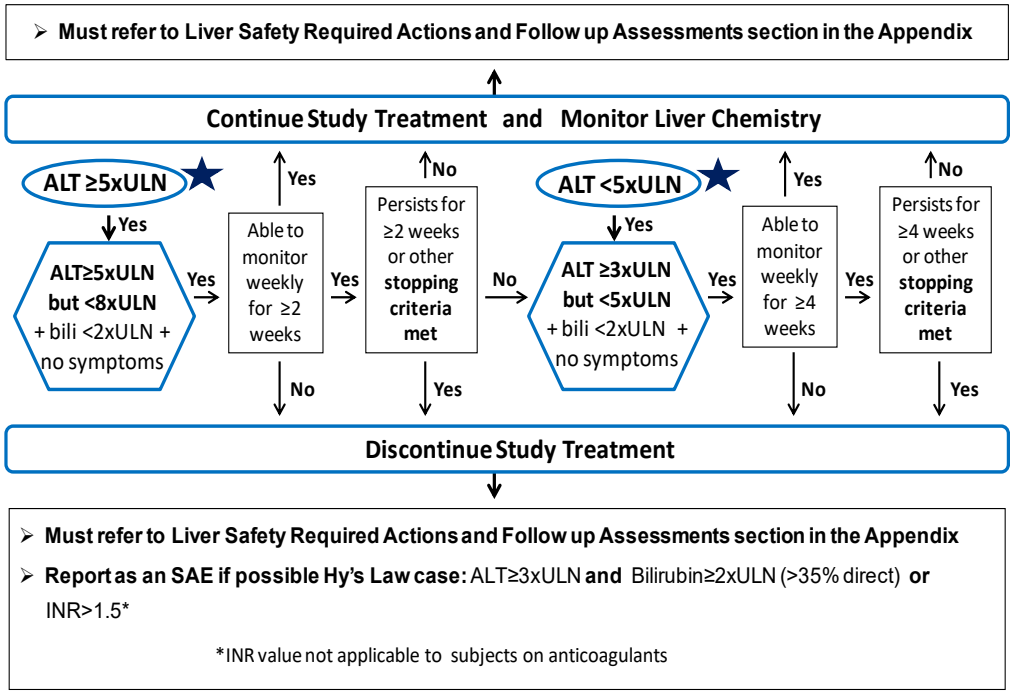
Phase III-IV liver chemistry stopping criteria 1-5 are defined below and Liver safety required actions and follow up assessments can be found in Appendix 6:

Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Abbreviations: ALT = alanine transaminase; bili = bilirubin; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Abbreviations: ALT = alanine transaminase; bili = bilirubin; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

7.1.1.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.1.2. QTc Stopping Criteria

- QTc(f) QT correction (Fredericia) formula *must* be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

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

- QTc stopping criteria are
  - QTc(F)>500 msec or uncorrected QT>600 msec
  - Change from baseline: QTc(F) > 60 msec
  - For patients with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc (F) with Bundle Branch Block	**Discontinuation QTc (F) with Bundle Branch Block**
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

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

7.1.3. Temporary Discontinuation

If a participant becomes infected with a parasitic infection whilst receiving study intervention and does not respond to anti-helminth treatment, temporary discontinuation of study intervention should be considered in consultation with GSK Medical Monitor.

7.1.4. COVID-19 testing

Participants that test positive for COVID-19 do not have to discontinue study intervention. Participants are encouraged to remain in the study and be followed up per study schedule as participants well-being allows. Effort should be made by the Investigator/site staff to keep the participant in the study until their nominal 24 weeks post initiation of investigational product.

- COVID-19 tests during the study may be performed, as determined by the investigator or local guidelines.
- All positive COVID-19 tests should be reported on the COVID-19 eCRFs and the AE/SAE eCRFs, as appropriate.
- Participants that test positive for COVID-19 do not have to discontinue study intervention.
- Positive tests should be reported to the appropriate local government authorities, per local regulations.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants who permanently stop study intervention are not required to withdraw from the study. If for any reason a participant must permanently stop study intervention every effort should be made by the PI/staff to keep the subject in the study to collect important efficacy and safety data.

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an end of study visit should be conducted, as shown in the SoA. See SoA for data to be collected at the

time of study discontinuation and end of study for any further evaluations that need to be completed.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Reasons for withdrawal must be captured in the eCRF and can include: an adverse event, lost to follow-up, protocol violation, lack of efficacy, sponsor terminated study, non-compliance, pregnancy, abnormal liver function test, abnormal laboratory results including clinically significant abnormality identified on ECG over-read.

7.3. Lost to Follow Up

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

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 100 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

8.1.1. Efficacy Endpoints

Primary Efficacy Endpoint

Not applicable

Secondary Efficacy Endpoint

- Number of clinically significant exacerbations
- Number of exacerbations requiring hospitalization or ED visits
- Number of exacerbations requiring hospitalization
- Change from baseline in clinic pre-bronchodilator FEV_1 at week 24
- Change from baseline in clinic post-bronchodilator FEV_1 at week 24
- Change from baseline in ACQ-5 score at week 24
- Change from baseline in morning PEF during weeks 20 – 24

CCI

8.1.2. Number of clinically significant exacerbations (including exacerbations requiring hospitalization or ED visits)

Clinically significant exacerbations of asthma as defined by:

> Worsening of asthma which requires use of systemic corticosteroids[1] and/or hospitalisation and/or Emergency Department (ED) visits.
>
> [1]*For all subjects, i.v. or oral steroid (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.*

Clinically significant exacerbations of asthma will be defined as the worsening of asthma which requires use of systemic corticosteroids. Exacerbation will be treated per the investigator's clinical practice protocol with the use of oral or parenteral corticosteroids.

Clinically significant exacerbations recorded in the eCRF by the Investigator or designee will be verified using data from the eDiary to confirm that the exacerbation was associated with changes in peak flow, rescue medication use, nocturnal awakening due to asthma symptoms requiring rescue medication use or worsening of asthma symptom score. In the case that an event described as a clinically significant exacerbation is not associated with deterioration in at least one of these objective eDiary parameters, the investigator will be asked to provide an explanation to support the decision for defining the event as an exacerbation. In those circumstances where the event cannot be supported by any objective assessment, the case will not be included as a protocol defined exacerbation but will be included as an investigator defined exacerbation. This verification process will be overseen by GSK clinical staff to ensure consistency.

For safety reasons alerts will be programmed into the eDiary to encourage the participant to contact the investigator if their asthma worsens (see Appendix 9). However, an alert in itself will not be classified as a clinically significant exacerbation.

8.1.3. Pulmonary Function Testing including Reversibility using the Maximum Post-Bronchodilator Method

Spirometry will be conducted, using the Spirometry equipment provided by GSK through a designated central laboratory at the visits specified in the Time and Events schedule. The spirometer should meet American Thoracic Society standards and produce a printout of all data generated, which should be stored in the participant's notes. The spirometer should be calibrated in accordance with the manufacturer's instructions and a calibration log maintained. Participants should withhold short-acting beta-$_2$-agonists (SABAs) for ≥6 hours and LABAs for ≥12 hours prior to clinic visit. Assessments to be recorded will include FEV_1, and FVC.

Pre-bronchodilator measurements will be taken at baseline, week 8, 16, and 24. In addition, at visit specified in the Time and Events schedule, post-bronchodilator values will be recorded following reversibility testing, using the maximum post bronchodilator method. For participants unable to achieve ≥12% reversibility and 200mL change at Visit 1 (screening), reversibility can be repeated at Visit 2 (Week 0). The procedures to achieve the maximum post-bronchodilator are those generated by the Asthma Clinical Research Network. Further details of spirometry and reversibility testing procedures are presented in the SRM.

8.1.4. eDiary

The participant will be asked to record the following parameters daily in the eDiary from Visit 1 (screening) onwards:

- Morning peak flow (best of three), before rescue medication usage (L/min)
- Number of puffs of rescue usage over the previous 24-hours
- Asthma symptom score over the previous 24-hours using a 6-point scale (Appendix 8)
- Frequency of awakening due to asthma symptoms requiring rescue medication use.
    - Daily dose of OCS

The participant will be asked to complete the ACQ-5 weekly in the eDiary from Visit 1 (screening) onwards.

From Visit 1 (screening) to Visit 2 (Week 0) only, participants will record peak flow twice a day to allow for calculation of PEF diurnal variability.

Alerts indicative of worsening asthma will be programmed into the eDiary (See Appendix 9). Sites will view participant data regularly through a study specific web portal.

eDiary data will additionally be reviewed at each clinic visit by the site staff throughout the treatment period.

Note: That an alert in itself will not qualify as a clinically significant exacerbation and the site should follow up with the participant as appropriate.

Participants will also be issued a paper worksheet to record adverse events and concomitant medications during the study. This will be used to assist participant recall in discussions with the investigator, for site staff to then enter as appropriate in the eCRF.

8.1.5. Asthma Control Questionnaire-5 (ACQ-5)

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of participants' asthma control that can be quickly and easily completed in clinical practice (Juniper, 2005). The questions are designed to be self-completed by the participant. The five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze). The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. The ACQ-5 score is a mean of the values recorded for the individual questions.

Throughout the study participants should complete the ACQ-5 on a weekly basis using their eDiary.

The participant should complete the questionnaire within the eDiary. The participant should be instructed to complete the questions as accurately as possible. The participant should be reassured that there are no right or wrong answers. If the participant requests help or clarification with any of the questions, he/she will be asked to re-read the instructions and give the answer that best reflects how he/she felt over the previous week. The investigator should not provide the participant with any answer or attempt to interpret any portion of a question.

If the ACQ-5 is completed through the eDiary while the participant is at a scheduled in clinic Visit, it is recommended that the ACQ be administered at the same time during the visit. To avoid biasing responses, the participants should not be told the results of diagnostic tests prior to completing the questionnaire and should be completed before any procedures are performed on the participant to avoid influencing the participants' response. Adequate time should be allowed to complete all items on the ACQ.

8.1.6. Clinician/Participant Rated Response to Therapy

The clinician and the participant will be asked to rate the response to therapy at the visits specified in the Time and Events schedule relative to the participant's asthma at Visit 2 (immediately prior to the first dose of mepolizumab). This is an overall evaluation of response to treatment, conducted separately by the investigator and the participant using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

- 1 = CCI [redacted]

- 2 = CCI [redacted]
- 3 = CCI [redacted]
- 4 = CCI [redacted]
- 5 = CCI [redacted]
- 6 = CCI [redacted]
- 7 = CCI [redacted].

The clinician or participant will indicate their response on a paper questionnaire which will be transcribed into the eCRF by study designated site staff.

8.1.7. Work Productivity and Activity Impairment Questionnaire: General Health (WAPI-GH)

Asthma has a substantial effect on lost days of works, with millions of days being lost each year (Catley, 2011). Furthermore, asthma results in lost productivity due to decreased effectiveness while working (Wilson, 2012). The WPAI-GH is a self or interviewer administered tool comprised of 6 questions which address absenteeism, presenteeism (reduced effectiveness while working), overall work productivity loss (absenteeism plus presenteeism), and activity impairment. This validated tool captures data from the past 7 days. WPAI-GH outcomes are scored as impairment percentages, with a higher percentage indicating greater impairment and less productivity (Reily Associates, 2018).

Participants will initially complete the paper questionnaire, and then the study designated site staff will transcribe the information into the eCRF.

8.2. Safety Assessments

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

8.2.1. Safety Endpoints

- Adverse Events, including both systemic (i.e., allergic/IgE-mediated and non-allergic) and local injection site reactions reported throughout the 24-week treatment period.
- Assessments include Physical examination, vital signs, Electrocardiogram, and laboratory evaluation.

8.2.2. Physical Examinations

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

- A brief physical examination will include, at a minimum, assessments of the abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Detailed nasal examination for presence or absence of nasal polyps will be performed.

8.2.3. Vital Signs

- Oral/ Axillary temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.4. Electrocardiograms

- Electrocardiogram measurements will be made after the participant has rested in the supine position for 5 minutes. The ECG should be obtained before lung function testing followed by other study procedures. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.
- A single twelve-lead ECG will be obtained at each timepoint specified in the Schedule of Activities (Section 1.3). If a routine single ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period (eg: 5-10 mins), and then use the averaged QTc values of the three ECGs to determine whether the patient should be discontinued from the study.

  Refer to Section (Section 7.1.2) for QTc withdrawal criteria.
- Paper traces are required to be maintained at the site with other source documents.

8.2.5. Steroid withdrawal examination review, where applicable

- Assessment of steroid withdrawal (i.e. the signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension) will be performed as outlined in the SoA.

8.2.6. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.2.7. Suicidal Ideation and Behaviour Risk Monitoring

This is not applicable to this study.

8.3. Adverse Events and Serious Adverse Events

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

The following adverse events of special interest will have customized AE and SAE pages in the eCRF:

- Systemic reactions
- Local injection site reactions

In addition, the investigator will be requested to assess events they consider systemic reactions against diagnostic criteria of anaphylaxis, and record in the CRF whether an event met the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] and in Appendix 7

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

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

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

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 4 months after the last dose.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed as per SAE reporting timelines.

8.4. Treatment of 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.

In the event of an overdose, the investigator/ treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until mepolizumab can no longer be detected systemically (at least 90 days).
3. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamics parameters will not be evaluated in this study.

8.7. Genetics

Genetics will not be evaluated in this study.

8.8. Biomarkers

Biomarkers will not be evaluated in this study.

8.8.1. Immunogenicity Assessments

Antibodies to mepolizumab will be evaluated in serum samples collected from all participants according to the SoA. An attempt will be made to collect the serum sample at the IP discontinuation visit or end of study visit from participants who discontinued study intervention or were withdrawn from the study.

Serum samples will be analysed with validated analytical methods using a tiered approach: screening, confirmation, titration and neutralizing analysis. Positive screening samples will continue with the confirmation analysis. Positive confirmation samples will be reported as positive for ADA. Positive confirmation samples will be evaluated for a relative assay binding response to report a titer value and whether the antibody response contains neutralizing antibodies.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal hypothesis testing is considered.

9.2. Sample Size Determination

The primary objective of the study is to evaluate the safety and tolerability of mepolizumab over 24 weeks of treatment. The primary endpoint is incidence of AEs, SAEs and AESIs. Sample size is determined based on the calculation of the probability of observing an AE. Table 3 provides the probabilities of observing various numbers of AEs based on a series of theoretical risks of an event occurring in a given patient in a study of 24 weeks duration, given a sample size of 100. For example, for a theoretical risk of an AE of 2/100 (true proportion value of 0.02) in this 24-week study, we would have a greater than 86% chance of observing at least one subject having the AE.

Table 3 Probabilities of observing a given number of subjects experiencing an adverse events or more (k) for given anticipated risks for a sample size of 100 patients

Theoretical Risk of an Event*					
K	**0.05**	**0.03**	**0.02**	**0.01**	**0.005**
1	0.9941	0.9524	0.8673	0.6340	0.3942
2	0.9629	0.8053	0.5967	0.2642	0.0898
3	0.8817	0.5802	0.3233	0.0794	0.0141
4	0.7422	0.3528	0.1411	0.0184	0.0017
5	0.5640	0.1821	0.0508	0.0034	0.0002
6	0.3840	0.0808	0.0155	0.0005	≤ 0.0001
7	0.2340	0.0312	0.0041	≤ 0.0001	≤ 0.0001
8	0.1279	0.0106	0.0009	≤ 0.0001	≤ 0.0001
9	0.0631	0.0032	0.0002	≤ 0.0001	≤ 0.0001
10	0.0282	0.0009	≤ 0.0001	≤ 0.0001	≤ 0.0001

*Theoretical risk of an event occurring in a given patient in a study of 24 weeks duration.

Assuming a 35% screen failure rate approximately 154 participants will be required to be screened in order for 100 participants to be enrolled onto the study treatment

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants enrolled and for whom a record exists on the study database. This population will be used for summarizing reasons for screen and run-in failures.
Safety	All participants who take at least 1 dose of study intervention. This population will be used for all safety, efficacy and health outcomes analyses.

9.4. Statistical Analyses

All analyses of safety data and efficacy data will be generated for the Safety Population. Additionally separate subgroup analyses will also be generated by with/without baseline maintenance OCS use (with separate summaries in those participants receiving maintenance OCS at baseline and those not maintenance OCS at baseline).

The study Statistical Analysis Plan (SAP) will be finalised prior to database lock which will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important primary, secondary and exploratory endpoints.

9.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

The study estimands are defined within Section 3 (Objectives and Endpoints). Further details regarding the estimation of each estimand is defined within the table below.

Endpoint	**Statistical Analysis Methods**
Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and grouped by body system and preferred term. The number and percentage of participants experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented. Separate summaries will be provided for all AEs, drug related AEs, fatal AEs, non-fatal SAEs, adverse events of special interest (AESIs) and AEs leading to withdrawal. Deaths and SAEs, if applicable, will be documented in case narrative format. Adverse events of special interest will include both systemic (i.e., allergic/IgE-mediated and non-allergic) and local injection site reactions for which further details will be collected through targeted eCRF pages. In addition, Vital Signs, 12 Lead ECG, Laboratory and Immunogenicity data will be summarised using a treatment policy strategy for the intercurrent event of treatment discontinuation, therefore reporting all data collected until study completion or withdrawal.	

9.4.2. Efficacy Analyses

All efficacy analyses will be performed on the Safety Population.

The study estimands are defined within Section 3 (Objectives and Endpoints). Further details regarding the estimation of each estimand is defined within the table below.

Taking prohibited medication during the treatment period is an important protocol deviation (PD) and will be included in the PD summary. However, this is not considered as an intercurrent event for the estimands defined within this study.

Endpoint	**Statistical Analysis Methods**
Primary	Not applicable
Secondary	• The number of clinically significant exacerbations (including exacerbations requiring hospitalization or ED visits) will be analysed using Negative Binomial regression via generalised estimating equations with a covariate of time period (pre-, post-mepolizumab) with follow-up time within each period included as an offset within the model. The exacerbation rates during the pre- and post-treatment with mepolizumab will be presented, including rate ratio comparing of pre- and post-mepolizumab periods and presented with

Endpoint	Statistical Analysis Methods
	corresponding 95% confidence interval. A treatment policy strategy will be utilised for the intercurrent event of treatment discontinuation. The period of time for which exacerbation information will be included in the post-mepolizumab period will be from the start of treatment until the week 24 visit, regardless of treatment discontinuation. For those participants with premature study withdrawal, the time period will include from the start of treatment until the date of withdrawal. Missing data (following early withdrawal) will be assumed to be missing at random (MAR) following subject withdrawal from the study. Analyses will also be conducted separately using the same analysis model and period definitions for exacerbations requiring hospitalization/ED visits and also exacerbations requiring hospitalization. • Analysis of change from baseline in clinic pre- bronchodilator FEV_1 and post-bronchodilator FEV_1 at Week 24 will be performed analysed as separate endpoints using a mixed models repeated measures (MMRM) analyses, allowing for covariates of visit, baseline maintenance OCS use (yes, no) and exacerbations in the year prior to the study (as an ordinal variable). All data will be included in the endpoint analysis will be from the start of treatment until the week 24 visit, regardless of treatment discontinuation. Mean change from baseline in FEV_1 will be summarised and presented with 95% confidence interval by visit. Comparisons will be Week 24 vs. Baseline, and all data collected up to and including Week 24, including participants who have discontinued study treatment, will be included in the analyses. Missing data (following early withdrawal) will be assumed to be missing at random (MAR) following subject withdrawal from the study. • Analysis of change from baseline in ACQ-5 score will be performed using a mixed models repeated measures (MMRM) analysis, allowing for covariates of visit, baseline maintenance OCS use (yes, no) and exacerbations in the year prior to the study (as an ordinal variable). All data will be included in the endpoint analysis will be from the start of treatment until the week 24 visit, regardless of treatment discontinuation. Mean change from baseline in ACQ-5 score will be summarised and presented with 95% confidence interval by visit. Comparisons will be Week 24 vs. Baseline, and all data collected up to and including Week 24, including participants who have discontinued study treatment, will be included in the analyses. Missing data (following early withdrawal) will be assumed to be missing at random (MAR) following subject withdrawal from the study. • Analysis of change from baseline in morning PEF during Weeks 20 –

Endpoint	Statistical Analysis Methods
	24 will be performed using a mixed models repeated measures (MMRM) analysis, allowing for covariates of visit, baseline maintenance OCS use (yes, no) and exacerbations in the year prior to the study (as an ordinal variable). All data will be included in the endpoint analysis will be from the start of treatment until the week 24 visit, regardless of treatment discontinuation. Mean change from baseline in PEF will be summarised and presented with 95% confidence interval by analysis period. Comparisons will be Weeks 20–24 vs. Baseline, and all data collected up to and including Weeks 20–24, including participants who have discontinued study treatment, will be included in the analyses. Missing data (following early withdrawal) will be assumed to be missing at random (MAR) following subject withdrawal from the study.

CCI

[redacted]

9.4.3. Health Outcomes Analyses

All health outcome analyses will be performed on the Safety Population.

Statistical Analysis Methods
Clinician and Participant-Rated response to therapy and WPAI-GH composite scores at week 24 will be summarised using a treatment policy strategy for the intercurrent event of treatment discontinuation, therefore reporting all data collected until study completion or withdrawal. No statistical analysis will be performed.

9.5. Interim Analyses

An analysis to present cumulative data may be completed if required.

9.5.1. Data Monitoring Committee (DMC)

Data Monitoring Committee is not used for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

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

10.1.5. Committees Structure

Not applicable for this study.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or

abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

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

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 30 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Data Management Plan.

10.1.9. Study and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Additional serum or urine pregnancy tests will be performed at all clinic visits per SoA and as determined necessary by the investigator to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [non fasting-Random][2]	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen by			

Laboratory Assessments	**Parameters**
	dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Highly sensitive Serum/ urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) • Serology- hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody The results of each test must be entered into the CRF.
Immunogenicity test	• Antibodies to mepolizumab will be evaluated in serum samples collected from all participants

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Investigator may ask for fasting and post prandial blood sugar examination at his/her discretion should random sample shows clinically significant value

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

10.3.1. Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition. • The disease/disorder being studied or expected progression, signs, or symptoms of

Events NOT Meeting the AE Definition
the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
o Results in death
o Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are

AE and SAE Recording
requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any significant updated / additional information in the SAE report section of the pdf,, scan and forward to GSK as a follow up report within 24 hours of awareness of the additional information. • A minimum of up to 3 attempts to follow up within 3 weeks after the last visit to be done by the site before case closure • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology subject to conduct of post mortem, within 24 hours of awareness of this information.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. Alternatively, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI- CTCAE) version 4.03 or updated will be used to evaluate AE and SAE

Assessment of Causality

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

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will try to provide GSK with a copy of any post-mortem findings including histopathology
- New or updated information will be recorded in the originally completed CRF.

Follow-up of AE and SAE
• The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK
• The primary mechanism for reporting SAE to GSK will be via email. • Site will use the Table 5 format (GSK SAE report) in order to report the event within 24 hours of occurrence. • The site will enter the SAE data into the electronic system case report form (eCRF) of the CRO as soon as it becomes available and a pdf copy of completed SAE pages along with relevant pages of eCRF which contain same information mentioned in Table 5 format (GSK SAE report) will be sent to GSK for reporting the SAE. Details of SAE reporting with contact information will be captured in the Study Reference Manual (SRM). • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic case report form (eCRF)will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic case report form (eCRF) has been taken off-line, then the site can report this information to the medical monitor/SAE coordinator by telephone. • Contacts for SAE reporting can be found in Title page. • The regulatory definition of Day 0 is the day when GSK or its agents first become aware of a valid case. • All SAEs must be submitted to CDSCO in Table 5 format (GSK SAE Report). . • PSRIs (Periodic Safety Report for Investigators) are uploaded by Global Safety in Veeva Clinical Operations Vault (COV). Veeva SRD (Safety Report Distribution) disseminates PSRIs to sites directly (SRD uses e-track contact for dissemination). • Soft / Hard copies of PSRIs will be sent to the sites by TO for EC notification.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP

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

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

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3. Collection of Pregnancy Information:

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention 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.

Any female participant who becomes pregnant while participating will be withdrawn from the study

10.5. Appendix 5: New York Heart Association Functional Classification of Congestive Heart Failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Adapted from American Heart Association, 2017

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology

Phase III-IV liver chemistry stopping criteria and required follow up assessments

<table>
<tr><td colspan="3">Liver Chemistry Stopping Criteria</td></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 8Xuln</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td colspan="2">ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td colspan="2">ALT ≥ 3xULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><td colspan="3">Required Actions and Follow up Assessments</td></tr>
<tr><td colspan="2">Actions</td><td>Follow Up Assessments</td></tr>
<tr><td colspan="2">• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline i.e. Visit 3 (see</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B DNA and Hepatitis delta antibody[5].
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total</td></tr>
</table>

Liver Chemistry Stopping Criteria	
MONITORING below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix 6) • If restart/rechallenge **not allowed or not granted**, permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline i.e. Visit 3 • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline i.e. Visit 3	bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5 which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

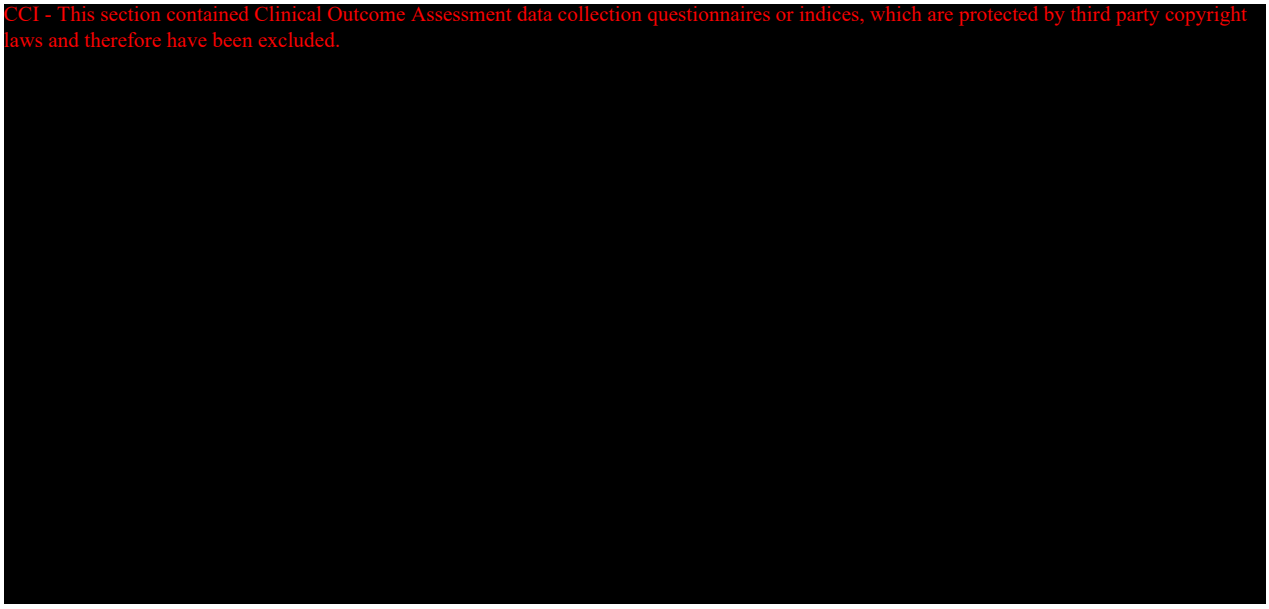
Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention. Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline i.e. Visit 3 • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline i.e. Visit 3.

10.7. Appendix 7: 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:

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

10.8. Appendix 8 : Daily Asthma Symptom Score



10.9. Appendix 9 - Criteria for e-Diary Alerts Indicative of a Potential Asthma Worsening

Criteria[1]	**Definition**
1	Mean AM PEF <80% of baseline stability limit
2	Mean asthma-related night time awakenings >50% increase over the baseline period (per night), >150% of the baseline mean
3	Rescue medication use requiring 4 or more puffs/day above the mean baseline value for any 2 consecutive days in the prior week, or 12 puffs or more on any one day in the prior week
4	Change in ACQ-5 **≥ +0.5** from the prior month OCS dose assessment
5	Symptoms of adrenal insufficiency

1. Baseline means for AM PEF, night time awakenings, and rescue medication use are calculated on a per night or per day basis using participant diary information from the 7 days prior to Visit 2

10.10. Appendix 10: Study Procedures during COVID-19 Pandemic

Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.
This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity. These measures will remain in place until the site is able to resume normal working activities.

Please reference Protocol Section 7.1.4 for further details regarding COVID-19 testing.

- COVID-19 tests during the study may be performed, as determined by the investigator or local guidelines.
- All positive COVID-19 tests should be reported on the COVID-19 eCRFs and the AE/SAE eCRFs, as appropriate.
- Participants that test positive for COVID-19 do not have to discontinue study intervention.
- Positive tests should be reported to the appropriate local government authorities, per local regulations.

Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the COVID-19 pandemic, sites should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when considering the need for a participant to attend the site for a visit.

For the duration of these special circumstances, home healthcare visits (home visits and telemedicine visits; see below) may be implemented for scheduled visits from Visit 3 onwards for participants unable to attend a site visit due to COVID-19 related restrictions.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants::

- Clinical investigators should document in site files and in participant notes/Electronic Heath Records as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes, and indicate

which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).

- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation and captured within the eCRF COVID-19 study impact forms. Visits that were conducted via the telephone will not be classified as missed visits; however, missed assessments (e.g. spirometry) should be recorded as COVID-19 protocol deviations and captured within the eCRF COVID-19 study impact forms.

Home Healthcare

Home healthcare is defined as:

- Visits at the participant's home, and
- Telemedicine visits.

Where applicable country and local regulations and infrastructure allow, home health care can be performed at the discretion of the investigator and following the participant signing of an informed consent form specific for home healthcare.

Home visits at the participant's home

These are performed at the participant's home by qualified home healthcare personnel (e.g., nurse) when the participants is unable to attend a site visit due to COVID-19 restrictions and the Investigator deems that a site visit is not necessary.

Telemedicine visits

These are defined as online (virtual) visits which use secure video conferences, phone calls, or a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress and safety. Telemedicine visits are conducted by an investigator or designee and may be done in combination with a home visit by a qualified personnel/ nurse.

The study investigator is responsible for ensuring that the identification, management, and reporting of exacerbations, AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/site staff or may be identified during interactions with the participants via telemedicine visits. In addition, healthcare personnel who are visiting participants at home may identify AEs as well and report them to the investigator for evaluation.

The participant should be informed of the home healthcare plan and any potential risks associated with home visits and telemedicine. The participant must sign an informed consent form specific to home healthcare.

IRB/Ethics committee should be informed of the introduction of home healthcare in the study. The committee should approve the home healthcare plan and the process should be documented in study files.

Study Intervention

The home healthcare personnel will be responsible for administering the study IP (at the discretion of the investigator) according to procedures detailed in the protocol.

Protocol Defined Procedures/Visits:

- Study participants in the Treatment Period of the study (Visit 2 to Visit 8 should be contacted by sites at each scheduled study visit to collect the following:
  - SAEs
  - AEs
  - Concomitant medication

  Note: the secondary objective of the study is to evaluate the efficacy of mepolizumab in participants with severe refractory asthma with elevated eosinophils. To evaluate the efficacy, the spirometry assessments "pre-bronchodilator FEV1 and post-bronchodilator FEV1" will be conducted. If the patient cannot come to site, the spirometry assessments can be conducted at home. It is the collective responsibility of Sponsor, site, and CRO to ensure that spirometers are available to conduct the home spirometry assessments and adequate training of the study personnel to conduct the assessments using all precautions and safety measures.
- The investigator shall contact their participants and intimate about the necessary precautions to ensure safety and wellbeing of the patients when encouraging them to visit the hospital. Investigator/designee staff need to stay in contact with the subject to ensure the end of study visit is completed within the prescribed window period (±7 Days).
- Where applicable country and local regulations (India) and infrastructure for home healthcare allows, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, ECG, spirometry, measurement of vital signs and weight, and preparation and administration of study drug (at the discretion of the Investigator). It is the responsibility of the investigator to inform Sponsor/CRO when this occurs and to document in source notes.
- Remote visits may be performed at the participant's home by qualified healthcare personnel and/or by relevant lab personnel and if the Investigator deems that a site visit is not necessary.
- Home visit will be done only after patient's consent for home visit to complete the study specific activities such as IP administration, spirometry and ECG procedures, as applicable.
- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the Investigator including in the participant's home, if deemed necessary.
- If visits to a site/home are not feasible, then the medical evaluation of condition may take place by Telemedicine visits using secure video conferences or phone calls as a way of communicating with and monitoring the participant's progress.

Sponsor/CRO will work together with the Investigator to ensure that the Site has the required equipment, training and support for this model.

Note: If the Investigator wishes to conduct a trial visit at a location that has not been previously assessed by GSK, it is the investigator's responsibility to identify an adequate alternate location and to notify GSK of the alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, is well-equipped to perform study procedures and covered by an adequate insurance. Furthermore, the investigator should have sufficient oversight to ensure that the staffs at the alternate location are trained to perform study procedures.

Study Intervention(s)

- Study teams should consider a home visit for administering the Investigational Medicinal Product (IMP) and rescue medication (if needed) to the participant. The process for this procedure (Subcutaneous injection of IMP) must be agreed with the site who will send the site personnel to perform the activity and adequately document in the IMP log.
- The Principal Investigator assumes Good Clinical Practice (GCP) responsibilities for IMP handling and the medical control for dispensing to patients. Site Staff should document the dispensing in the Dispensing/Accountability Logs adding a comment that this was a home visit.
  IMP includes study medication and ancillary supplies relating to IMP administration as needed.
- In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring.

Data Management/Monitoring:

- If on-site monitoring is no longer permitted, Sponsor/CRO will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, Sponsor/CRO will work with the site to ensure subject privacy.

- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing the EDC platform using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol,, eCRF requirements (with training documented), and the DoR log updated accordingly.

- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by Sponsor/CRO.

10.11. Appendix 11: Abbreviations and Trademarks

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NUCALA

Trademarks not owned by the GlaxoSmithKline group of companies
None

10.12. Appendix 12: Protocol Amendment History

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

Amendment 4 03-AUG-2022

Overall Rationale for the Amendment:

i) The requirement of oral corticosteroids (OCS) and associated phases (Induction phase, optimization phase, OCS reduction/Manitenance phase) has been removed.
ii) Inclusion criteria (S. no. 5) have been updated from the study to align with the current management practice of SEA which does not include use of stable OCS use for prolonged periods of time and the changes are in line with Prescribing information of the product.
iii) Stringency of spirometry timings (i.e. must be performed at the same time ±1 hour of the visit 1) has been removed.
iv) The recommendation of triplicate 12-lead ECG within 4 minutes duration has been removed.
v) The information for reporting SAE to GSK has been updated.

Amendment -3 17-MAR-2021

Overall Rationale for the Amendment:

i) As per recommendation by DCGI, Immunogenicity assessments have been added at Induction Phase, IP discontinuation Visit/End of Study Visit. Details of Immunogenicity testing provided

Amendment 2 05-NOV-2020

Overall Rationale for the Amendment:

i) The time point for IgE (total) are updated and testing for IgE (specific) is removed.

ii) The immunogenicity testing is no longer applicable for this study

iii) Changes in the spirometry assessments are made.

iv) Rescreened patients will be assigned a new screening number.

v) The guidance to conduct the study during COVID-19 pandemic is added.

Amendment 1 27-AUG-2019

Overall Rationale for the Amendment:

i) The sample size revised to 100 evaluable patients

(ii) In the inclusion criteria, the age of the patients to be enrolled is ≥18 years

(iii) IgE levels evaluated before screening of patients

11. REFERENCES

Agarwal R, Dhooria S, Aggarwal AN, et al. Guidelines for diagnosis and management of bronchial asthma: Joint ICS/NCCP (I) recommendations. Lung India. 2015;32(Supplement 1): S1-S42.

Agbetile J, Green R. New therapies and management strategies in the treatment of asthma: patient-focused developments. *J Asthma Allergy* 2011; 4:1-12.

Albers FC, Khurana S, Bradford E, et al. Long-term safety & durability of mepolizumab in life-threatening/seriously debilitating severe eosinophilic asthma (SEA): COSMEX. *Eur Resp J* 2018; 52: OA3566; DOI: 10.1183/13993003.congress-2018.OA3566

American Heart Association. Classes of Heart Failure. Available at: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp. Last Updated May 2017. Accessed on November 1, 2018

Barnes PJ, Jonsson B, Klim JB. The costs of asthma. *Eur Respir J* 1996; 9:636-42.

Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004; 170:836-44.

Bel EH, Wenzel SE, Thompson PJ, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. *N Engl J Med* 2014; 371:1189-97. DOI: 10.1056/NEJMoa1403291.

Catley MC, Coote J, Bari M, et al. Monoclonal antibodies for the treatment of asthma. *Pharmacol Ther* 2011;333-351.

Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43:343-373.

Cisternas MG, Blanc PD, Yen IH, et al. A comprehensive study of the direct and indirect costs of adult asthma. *J Allergy Clin Immunol* 2003;111(6):1212-18.

Clinical Investigator's Brochure (CIB) [GlaxoSmithKline Document Number CM2003/00010/07, SB-240563,Version No 11,Effective date 14-May-2012], and the Study Reference Manual (SRM)

Cohn L, Elias JA, Chupp GL. Asthma: mechanisms of disease persistence and progression. *Ann Rev Immunol* 2004 ;22:789-815.

Deeks ED. Mepolizumab: A Review in Eosinophilic Asthma. *BioDrugs* (2016) 30:361–370.

Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009; 180:817-22.

Gleich G, Klion A, Lee J, Weller P. The consequences of not having eosinophils. Allergy. 2013;68(7):829-835.

Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention, 2015. Available from: http://www.ginasthma.org/ Accessed on November 1, 2018.

Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360:973-84. [Erratum, *N Engl J Med* 2011;364:588].

Hankinson, JL, Odencrantz, JR, Feden, KB. Spirometric Reference Values from a Sample of the General U.S. Population. *AM J Respir Crit care Med*. 1999; 159:179-187.

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

Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14: 902–907.

Juniper EF, Svensson K, Mőrk AC, et al. Measurement properties and interpretation of three-shortened versions of the asthma control questionnaire. *Resp Med* 2005; 99:553-558.

Korn S, Both J, Matthias J. et al. Prospective evaluation of current asthma control using ACQ and ACT compared with GINA criteria. *Ann Allergy Asthma Immunol*. 2011 107(6): 474-9.

Le Gal F, Gordien E, Affolabi D, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol*. 2005;43(5):2363–2369.

Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.

National Institutes of Health (NIH). National Heart, Lung, and Blood Institute (NHLBI). National Asthma Education and Prevention Program. Expert Panel Report 3: guidelines for the diagnosis and management of asthma. August 2007. NIH publication no. 07-4051.

Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014 Jan 13;1:CD003559.

Ortega H, Bradford ES, Albers FC, et al. Long-Term Safety of Mepolizumab in Patients with Severe Eosinophilic Asthma: The COLUMBA Study *Am J Respir Crit Care Med* 2018;197:A1367.

Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380: 651-9.

Polosa R, Morjaria J. Immunomodulatory and biologic therapies for severe refractory asthma. *Respir Med* 2008; 102:1499-1510.

Reily Associates. Scoring of WPAI. Available at: http://www.reillyassociates.net/WPAI_Scoring.html. Accessed on November 1, 2018.

Robinson DS, Campbell DA, Durham SR, et al. Systemic assessment of difficult-to-treat asthma. Asthma and Allergy Research Group of the National Heart and Lung Institute. *Eur Respir J* 2003;22(3):478-83.

Robinson DS, Hamid Q, Ying S, et al. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992;326(5):298-304.

Rothenberg, ME. Eosinophilia. *N Engl J Med* 1998;338(22):1592-600.

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

Seminario M C and Gleich GJ. The role of eosinophils in the pathogenesis of asthma. *Curr Opin Immunol* 1994;6(6):860-4.

Sur S, Gleich GJ, Swanson MC, et al. Eosinophilic inflammation is associated with elevation of interleukin-5 in the airways of patients with spontaneous symptomatic asthma. *J Allergy Clin Immunol* 1995;96(5 Part 1):661-68.

Wardlaw, AJ, Brightling C, Green R, et al. Eosinophils in asthma and other allergic diseases. *Br Med Bull* 2000;56(4):985-1003.

Wenzel SE. Severe asthma in adults. *Am J Respir Crit Care Med* 2005; 172:149-160.

Wilson SR, Rand CS, Cabana MD. Asthma Outcomes: Quality of life. *J Allergy Clin Immunol* 2012; 129:S89-123.

Signature Page for 209682 TMF-14888313 v1.0

Reason for signing: Approved	Name: PPD Role: A Date of signature: 23-Aug-2022 07:54:08 GMT+0000

Signature Page for TMF-14888313 v1.0