TITLE PAGE

Protocol Title: A multi-center, randomized, double-blind, parallel-group, placebo-controlled study of mepolizumab 100 mg SC as add-on treatment in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels (Study 208657)

Protocol Number: 208657/ Amendment 6-STD

Compound Number:	SB240563

Study Phase: IIIA

Short Title: **M**epolizumab as **A**dd-on **T**reatment **IN** participants with COPD characterized by frequent **E**xacerbations and **E**osinophil Level

Acronym: MATINEE

Sponsor Name and Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

IND: 006971

EudraCT: 2018-001540-56

Approval Date: 06-DEC-2021

SPONSOR SIGNATORY:

Protocol Title: A multi-center, randomized, double-blind, parallel-group, placebo-controlled study of mepolizumab 100 mg SC as add-on treatment in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels (Study 208657)

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The signed page is a separate document.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment-6-STD	06-Dec-2021	TMF-13811028
Amendment-5-STD	16-Oct-2020	2018N357924_05
Amendment-4-STD	13-Sep-2019	2018N357924_04
Amendment-3-STD	18-Jul-2019	2018N357924_03
Amendment 2-CHI-1	23-May-2019	2018N357924_02
Amendment 1-USA-1	23-May-2019	2018N357924_01
Original Protocol	15-Feb-2019	2018N357924_00

Amendment 6: 06-DEC-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 6:

Non-pharmaceutical interventions (NPIs) taken to prevent COVID-19 transmission (e.g., masks, lockdowns, physical distancing) have led to an observed reduction in the rate of exacerbations among individuals with COPD. Given that the primary study outcome and eligibility criteria for this study are based on an exacerbation rate, the observed reduction in the rate of COPD exacerbations has affected (i) the collection of exacerbation data among enrolled participants and (ii) the recruitment of participants into the study, respectively.

The rationale for this amendment is two-fold. First, based on the presumption that the COPD exacerbation rate is expected to progressively return to pre-COVID-19 levels following the lifting of NPIs, this amendment will extend the allowable treatment duration to beyond 52 weeks and up to 104 weeks to maximize the opportunity for collection of exacerbation data. Second, to further mitigate the effects of a lower-than-expected exacerbation rate and to maintain sufficient study power, this amendment will permit the study population to increase up to 1400 participants, if warranted, based on future blinded sample size re-evaluations.

A summary of changes is described in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 - Schema	Schema was updated to reflect an extended treatment duration beyond 52 weeks and up to 104 weeks.	Updates to the treatment duration necessitated a change in the study schema.
Section 1.3 – Schedule of Activities (SoA)	A second SoA table was added (Section 1.3.2) to reflect procedures for participants enrolled in an extended treatment duration beyond 52 weeks and up to 104 weeks.	An extended treatment duration maximizes the opportunity for data collection on exacerbations.
	An explanation was added under Section 1.3 to differentiate the two SoA tables (Section 1.3.1 and Section 1.3.2) and explain when 'IP Conclusion' and 'Study Conclusion' dates will be communicated to the study sites.	To highlight the difference between the two SoA tables and that study sites will be provided with information to plan each participant's Exit Visit.
Section 1.1 – Synopsis Section 4.1 – Overall Design Section 9 – Statistical Considerations	Updates were made to the number of randomized participants, which can increase up to 1400 (approximately 700 per group).	Future blinded sample size re-evaluations may warrant an increase in the size of the study population to maintain sufficient study power.
Section 1.1 – Synopsis Section 4.1 – Overall Design Section 4.2 – Scientific Rationale for Study Design	Wherein treatment duration was discussed, updates were made to reflect the extension of the treatment duration to beyond 52 weeks and up to 104 weeks.	Changes were required to reflect the updated study design.
Section 1.1 – Synopsis	In the 'Overall Design', the first paragraph was updated to state the study treatment duration will be dependent on a number of factors discussed in Section 4.4.	To reference the section of the protocol that provides details related to study treatment durations for participants.

Section # and Name	Description of Change	Brief Rationale
Section 4.4 – End of Study Definition	Section was updated to include 'Completion of Intervention Period' and 'Completion of Study' definitions for participants enrolled for 52 weeks (Section 4.4.1) and those enrolled beyond 52 weeks and up to 104 weeks (Section 4.4.2). The 'End of Study' definition (Section 4.4.3) was updated to reference the SoA for 52 weeks (Section 1.3.1).	The updated study design (52 weeks versus beyond 52 weeks) warranted a differentiation of these definitions.
Section 1.3.1 – SoA for the First 52 Weeks	Table footer 'a' was updated, specifically point [2] under the note, to clarify that for participants with no historical eosinophil count, the blood sample collected at Visit 1 must be >14 days after Visit 0.	To further clarify the blood collection timepoint for participants with no documented historical eosinophil count.
	Table footer 'j' was expanded to additionally indicate that all medications and vaccines used at pre-screening/screening and during the study are to be recorded.	To ensure that concomitant therapies are recorded.
	Table footer 'r' was updated.	To clarify the assessment of AEs and SAEs throughout the study.
	'EXACT/ER-S:COPD' was replaced with 'Daily Symptom Diary' and the related table footer 't' was updated.	In addition to the EXACT instrument, daily symptom reporting includes other questions on symptoms, rescue medications, and night time awakenings (Section 8.1.3.3).

Section # and Name	Description of Change	Brief Rationale
Section 1.3.1 – SoA for the First 52 Weeks	Table footer 'w' was added.	To clarify that all procedures listed for Week 52 in the first SoA table (Section 1.3.1) apply only to participants enrolled for 52 weeks and not beyond.
	Table footer 'x' was added.	To explain that 'reconsent' only applies to participants enrolled prior to implementation of Protocol Amendment 6 and who have agreed to extend study participation beyond 52 weeks.
	Table footer 'y' was added.	To reiterate when home healthcare can be used and what study procedures qualify for it.
	Table footer 'z' was added.	To reiterate that participants will be monitored in clinic for 1 hour after receiving the first 3 doses of study intervention.
	Table footer 'aa' was added.	To state the permissibility of extension of visit windows for the screening/run-in period 'under exceptional circumstances' with advance written permission from GSK's Medical Monitor.
Section 8.1.3.3 – Evening eDiary	Section 8.1.3.3 was renamed 'Daily Symptom Diary' and the types of symptom collections were bulleted upfront.	The renaming of Section 8.1.3.3 associates the symptom reporting with the SoAs.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 – Synopsis	In the 'Overall Design', the 'note' discussing the impact of COVID-19 was updated.	To elaborate on the impact of COVID-19 and public health measures on the study.
Section 1.1 – Synopsis Section 4.1 – Overall Design	A statement was added that the PK sub-study in China and the US is to be conducted in the first 52 weeks of the study treatment period only.	To clarify when the PK sub-study is to be conducted.
Section 1.1- Synopsis Section 4.1 – Overall Design	The requirement for a minimum ICS dose of ≥500 mcg/day fluticasone propionate or equivalent for 3 months prior to Screening Visit 1 was reiterated.	To reiterate the study eligibility criteria with respect to the minimum required dose of ICS.
Section 5.1 – Inclusion Criteria	In the first paragraph, the SRM was cited for further details on the inclusion criteria.	To reiterate a relevant reference regarding interpretation of the inclusion criteria.
Section 5.3.2 – Randomization Exclusion Criteria	An additional randomization exclusion criterion was added (#6) related to 12-lead ECG.	To ensure that participants with a prolonged QT interval at Visit 2 are not randomized into the study.
Section 2.3.1 – Risk Assessment	For the mitigation strategy of 'blinding eosinophil counts', 'delegate' was added for monthly patient follow-up [i.e., Investigators (or delegate)] and 'specialized in COPD' was removed.	Patient follow-up will be with qualified personnel who may or may not be specialized in COPD care.
Section 2.3.2 – Benefit Assessment	In the third paragraph, the wording was changed to indicate that participants will be followed-up monthly rather than having to attend monthly visits.	To acknowledge that study procedures may not be conducted in clinic but could be conducted with home healthcare.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.3 – Overall Benefit: Risk Conclusion	A statement was added that participants will be receiving optimized maintenance COPD therapy throughout the study in addition to their randomized IP.	To reiterate a key aspect of the study design regarding participant safety and well-being.
Section 5.4 – Screen and Run-in Failures	The bullet regarding SAE data collection for screen failures at Visit 0 and Visit 1 was updated.	To clarify that, as per Section 8.3.1. and not related to China, prior to the start of study intervention, SAEs related to study participation or 'any GSK product' are to be collected from the time informed consent is signed.
	For run-in failures, the bullet regarding the collection of details on COPD medications in the 3 months prior to Screening Visit 1 was deleted.	Because run-in failures do not receive any study intervention, these data are not necessary.
	The last paragraph regarding re-screening of participants was updated.	To clarify that re-screening of both screen failure and run-in failure participants is permissible with written approval.
Section 6.3 – Measures to Minimize Bias: Randomization and Blinding	In the second paragraph, the mention of 13 doses of IP was removed.	Doses of IP will be greater than 13 for participants enrolled beyond 52 weeks.
Section 6.4 – Study Intervention Compliance	In the second and third bullets, the wording was updated to also reflect monitoring of participants during a home visit, if applicable.	To make the wording applicable to instances wherein home healthcare is used.
Section 6.5 – Concomitant Therapy	Inclusion of wording pertaining to COVID-19 vaccines.	To clarify the permissibility for participants to be vaccinated with authorized or approved COVID-19 vaccines.

Section # and Name	Description of Change	Brief Rationale
Section 7.2 – Participant Discontinuation/Withdrawal from the Study	A paragraph was added at the end regarding data handling if a participant withdraws from the study prior to their 'Completion of Study' date.	To indicate that participants will be considered as having missing data from the date of study withdrawal to the planned 'Completion of Study' date.
	'Home healthcare, if applicable' was included as an alternate to in-clinic visits for completion of specified visits for participants who have permanently discontinued IP but have not withdrawn consent.	Home healthcare may be used by study participants.
Sesction 8.2 – Safety Assessments	In the first paragraph, a statement was added to indicate the safety assessments (vital signs, safety laboratories) that will be taken at less frequent intervals in the second versus first year of the study.	The safety profile of mepolizumab in the IB justifies a less frequent assessment of safety measures after the first year of treatment.
Section 9 – Statistical Considerations	The first paragraph was updated to include 'annualized' exacerbations; 'over 52 weeks' was removed; and, 'intercurrent' was added to the statement "COVID-19 pandemic-related 'intercurrent' events".	To align with the updated study design and the wording in Section 9.4.1 (Efficacy Analyses) regarding strategies for 'intercurrent' events.
Section 9.2 – Sample Size Determination	Regarding the statement on the estimated annualized rate of moderate/severe exacerbations in the placebo arm of 1.7, it was clarified that this was based on studies conducted prior to the COVID-19 pandemic.	To provide a chronological context to the exacerbation rate originally used for the sample size calculation.

Section # and Name	Description of Change	Brief Rationale
Section 9.2 – Sample Size Determination	The paragraph related to blinded re-evaluations of the sample size was updated.	To indicate that blinded re-evaluations of the sample size will be conducted to ensure its adequacy, and the sample size may increase up to a potential maximum of 1400 participants.
Section 9.2.1 – Sample Size Sensitivity	Table 2 was updated to include lower annualized exacerbation rates (i.e., 0.9 and 1.1).	To provide information on the effect of annualized exacerbation rates lower than 1.3 on study power.
Section 9.4 – Statistical Analyses	In the first paragraph, it was added that additional analyses including the impact of COVID-19 on the study will be addressed in the RAP.	To reiterate that the RAP will include all relevant statistical analyses.
Section 9.4.1 – Efficacy Analyses	Regarding secondary endpoints and the proportion of responders at Week 52, the effect of restrictions due to COVID-19 was clarified as being 'on or before the Week 52 visit'.	Since the study is continuing beyond Week 52, this clarification was needed.
Section 10.1.3 – Informed Consent Process	The bullet regarding re-screening was updated. A bullet on the requirement and timeline to re-sign a new ICF for participants extending their treatment duration to beyond 52 weeks was included.	To clarify when rescreening and reconsenting are permissible or required, respectively.
Section 10.4.5 – Reporting of SAE to GSK	For 'SAE Reporting to GSK via Electronic Data Collection Tool', the bullet regarding review and verification of causality within 72 hours of SAE entry into eCRF was removed.	To reflect GSK's updated Monitoring SOP (VQD-SOP-005639).

Section # and Name	Description of Change	Brief Rationale
Section 10.10.2 – Study Procedures During COVID-19 Pandemic Section 1.3 – Schedule of Activities (SoA)	The SoA Table 4 (Assessments for clinic visits and home healthcare) was deleted and its mention removed. A row was included in the main SoA tables (Section 1.3) regarding home healthcare and procedures that qualify for it, including footer 'y' (Section 1.3.1) and footer 'j' (Section 1.3.2). In Section 10.10.2.1, 'Study assessments performed through home healthcare' was updated to cite SoA tables in Section 1.3.	To decrease the duplication of information.
	The qualifying timepoints for home healthcare were corrected from Visit 3 onwards to Visit 5 onwards.	In accordance with the risk mitigation strategies (Section 2.3.1), participants are to be monitored in clinic following the first 3 administrations of study product (i.e., Visits 2, 3, and 4).
Section 11 – References	The reference regarding the IB for mepolizumab was removed.	To ensure the study protocol does not cite an outdated IB.
Section 2.3 – Benefit/Risk Assessment Section 6.1 – Study Intervention(s) Administered	The citation to the IB was deleted and instead reference was made to the 'current version of the IB'.	
Throughout protocol	The term 'subject' was replaced with 'participant' where applicable. Minor editorial and document formatting revisions were made.	To align with GSK's protocol template.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A multi-center, randomized, double-blind, parallel group, placebo-controlled study of mepolizumab 100 mg SC as add-on treatment in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels (Study 208657)

Short Title: **M**epolizumab as **A**dd-on **Tr**eatment **IN** participants with COPD characterized by frequent **E**xacerbations and **E**osinophil Level (MATINEE)

Rationale: Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response, in the airways and the lung, to noxious particles or gases. While the disease course is marked by progressive deterioration in airflow it is punctuated by acute exacerbations of COPD (AECOPD) which contribute to the overall disease severity and which increase in frequency as the disease worsens [Vogelmeier, 2017; Barnes, 2015]. In addition to the increased risk of morbidity and mortality associated with COPD exacerbations, these events place a significant economic burden on healthcare systems which is predicted to increase with the increasing global disease prevalence [Halpin, 2017; Perera, 2012; Toy, 2010].

Mepolizumab has been studied in patients with COPD with limited or no treatment options [Pavord, 2017]. The initial Phase IIIA COPD mepolizumab program consisted of two 52-week multicenter, randomized, double blind, placebo-controlled studies, MEA117106 and MEA117113 [Pavord, 2017]. These studies compared treatment with mepolizumab to placebo when added to maximum inhaled standard of care (Inhaled corticosteroids [ICS] plus long-acting $beta_2$-adrenergic receptor agonists [LABA] plus long-acting muscarinic receptor antagonists [LAMA]). MEA117113 randomized participants with peripheral blood eosinophil counts of ≥150 cells/µL at Screening or ≥300 cells/µL in the prior 12 months. MEA117106 was stratified based on blood eosinophil levels at Screening and randomized participants who either met the same threshold as for MEA117113, designated the “high stratum”, or who had a blood eosinophil level <150 cells/µL at Screening and no evidence of blood eosinophil levels ≥300 cells/µL in the year prior, designated the “low stratum”.

Evidence from MEA117113 and MEA117106 demonstrated a consistent and clinically relevant impact of treatment with mepolizumab 100 mg SC compared with placebo on exacerbation reduction in participants with COPD who frequently exacerbate despite treatment with ICS-based inhaled triple maintenance therapy (ICS plus LABA plus LAMA).

This study is designed to confirm the benefits of mepolizumab treatment on the primary outcome of moderate/severe exacerbations as well as to more robustly inform on outcomes which are less frequent such as exacerbations requiring emergency department (ED)/hospitalization as well as additional important health related quality of life data.

Based on the results of the MEA117113 and MEA117106 studies and feedback from health authorities, the inclusion criteria for this study have been modified to focus on a group of COPD participants with a documented historical blood eosinophil count of ≥150 cells/μL in the 12 months prior to Screening Visit 0 (or at Screening Visit 1) and blood eosinophil counts of ≥300 cells/μL at Screening Visit 0 that are more likely to benefit from mepolizumab treatment.

Objectives and Endpoints:

Objective	Endpoint
Primary • To evaluate the efficacy of mepolizumab 100 mg subcutaneous (SC) compared to placebo, given every 4 weeks in liquid formulation by safety syringe (SS) to COPD participants at high risk of exacerbations despite the use of optimized COPD maintenance therapy.	• Annualized rate of moderate/severe exacerbations
Secondary • To evaluate mepolizumab 100 mg SC compared to placebo given every 4 weeks in liquid formulation by SS on additional efficacy assessments, health related quality of life (HRQoL), health care utilization, and symptoms	• Time to first moderate/severe exacerbation • Proportion of COPD assessment test (CAT) responders (≥2 unit reduction in CAT score from Baseline) at Week 52 • Proportion of St. George's Respiratory Questionnaire (SGRQ) total score responders (measured using the St. George's Respiratory Questionnaire for COPD [SGRQ-C], and defined as ≥4 point reduction in SGRQ total score from Baseline) at Week 52 • Proportion of Evaluating Respiratory Symptoms in COPD (E-RS: COPD) responders (≥2 unit reduction in total score from Baseline) at Week 52 • Annualized rate of exacerbations requiring ED visit and/or hospitalization

Overall Design:

This is a multi-center, randomized, placebo-controlled, parallel group, double-blind, trial evaluating mepolizumab 100 mg SC compared with placebo given every 4 weeks as a liquid formulation in a pre-filled safety syringe injection. The study treatment period will be a minimum of 52 weeks up to a maximum of 104 weeks. The study treatment duration for each participant will be determined based on a number of factors, which are detailed in the main body of the study protocol (Section 4.4).

Study inclusion criteria require a blood eosinophil count of ≥300 cells/µL at Screening Visit 0 and a documented historical blood eosinophil count of ≥150 cells/µL in the 12 months prior to Screening Visit 0. Historical blood eosinophil count used to meet inclusion criteria must not have been measured within 14 days of a COPD exacerbation. Participants with no documented historical blood eosinophil count of ≥150 cells/µL must meet this threshold at the Screening Visit 1 assessment. Participants must have a history of regular use of ICS-based triple maintenance COPD therapy (as defined in Inclusion Criteria, Section 5.1) for at least 12 months prior to Screening Visit 1. In addition, for at least 3 months immediately prior to Screening Visit 1, each participant must have a documented history of use of a specific ICS-based inhaled triple maintenance COPD regimen (ICS plus LABA plus LAMA) with a minimum inhaled corticosteroid at a dose of ≥500 mcg/day fluticasone propionate or equivalent. Participants are also required to have a history of at least 2 moderate COPD exacerbations that were treated with systemic corticosteroids (intramuscular (IM), intravenous or oral) with or without antibiotics, or 1 severe exacerbation requiring hospitalization in the 12 months prior to Screening Visit 1 and one of the exacerbations has to have occurred while treated with ICS plus LABA plus LAMA. All participants will continue optimized maintenance COPD therapy throughout the entire duration of the study regardless of intervention arm assignment.

Note: The COVID-19 pandemic has impacted the conduct of this clinical study by, for example, preventing participants from attending study visits at the study site during periods when the transmission of the virus is being managed with local/national government instruction to not leave home. Where applicable country and local regulations and infrastructure allow, and at the discretion of the Investigator and consent of the participant, home healthcare may take place at a location other than the clinical study site, e.g., the participant's home to perform study assessments. In addition, the public health measures brought in to combat COVID-19 such as mask wearing, social distancing and lockdowns can potentially lead to a fall in non-COVID viral infections (e.g., respiratory syncytial virus, influenza) and pollution, which in turn reduce the overall COPD exacerbation rates of the study population.

Disclosure Statement:

This is a parallel group double-blind intervention study with 2 arms, one active mepolizumab and one placebo matching arm given to participants as an add on to their optimized maintenance COPD therapy.

Number of Participants:

It is estimated that approximately 4000 participants will be screened to achieve approximately 800 randomized participants and an estimated total of 400 randomized participants per intervention group. The number of randomized participants may increase up to approximately 1400 (approximately 700 per intervention group) following blinded sample size re-evaluation.

Intervention Groups and Duration:

Following the Run-in period, eligible participants will be randomized 1:1 to mepolizumab or placebo. Interventional Product (IP) will be administered as a single SC injection given every 4 weeks.

Excluding screening and run-in periods, participants will remain in the study for at least 52 weeks and either up to 104 weeks or until a scheduled visit that aligns to the date the last randomized participant is scheduled to complete their Week 52 Exit Visit, whichever is sooner. The timing of the last randomized participant into the study will thus affect the timing of the Exit Visit for participants enrolled beyond 52 weeks. All participants will be expected to complete at least 52 weeks of the study. The last randomized participant will be scheduled to complete only 52 weeks of the study.

The primary efficacy endpoint will include all moderate (require either systemic corticosteroids and/or antibiotics) and severe exacerbations (requiring hospitalization or resulting in death) reported after the first dose up to and including the last study visit (Exit Visit).

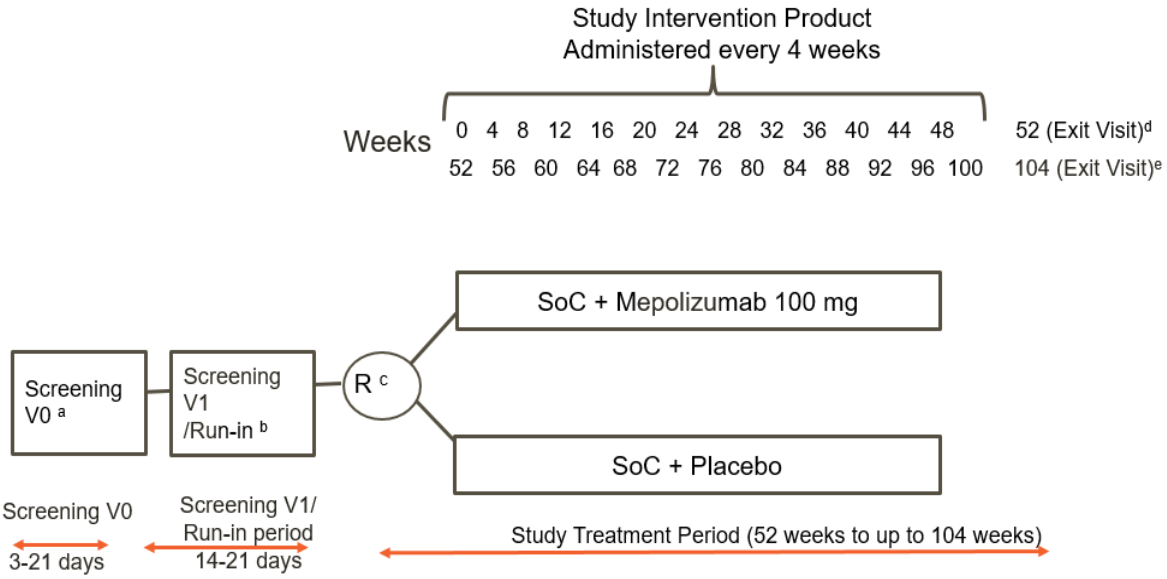
Pharmacokinetic Sub-study: China and US only

An optional pharmacokinetic (PK) sub-study will be conducted in China and the US to assess potential ethnic differences in the PK of mepolizumab 100 mg, in liquid formulation, between non-Asian participants in the US and Chinese participants in China. PK blood samples will be collected from approximately 50 randomized participants from the US and approximately 50 randomized participants from China to ensure at least 20 participants from each country provide PK information related to mepolizumab. This PK assessment will be conducted over the first 52 weeks of the study period only.

Independent Adjudication Committee:

An independent external adjudication committee for all serious adverse event (SAE) reports will be utilized in this study to ensure external objective medical review of these events in a blinded fashion. Additionally, Major Adverse Cardiac Events (MACE) (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) will also be adjudicated in a blinded fashion by the independent external adjudication committee.

1.2. Schema



[a] Participants must have an eosinophil count of ≥300 cells/µL at Screening Visit 0 to proceed to Visit 1. They are also required to have a documented historical eosinophil count of ≥150 cells/µL in the 12 months prior to Screening Visit 0.
[b] Participants with no historical eosinophil counts of ≥150 cells/µL must have an eosinophil count ≥150 cells/µL at Screening Visit 1.
[c] R = Randomization: Randomization criteria should be assessed at Week 0 (Visit 2) prior to randomization.
[d] For participants enrolled in the study for 52 weeks, the Exit Visit will be at Week 52, 4 weeks after the last dose; see Section 4.4.
[e] For participants receiving study treatment beyond 52 weeks, the Exit Visit will be at Week 104 or aligned to the date the last randomized participant is scheduled to complete their Week 52 Exit Visit, whichever is sooner; see Section 4.4. The Exit Visit will be 4 weeks after the last dose.

1.3. Schedule of Activities (SoA)

Two SoA tables are shown below, which describe study procedures to be followed (i) for the first 52 weeks for all participants and for participants with an Exit Visit at Week 52 (Section 1.3.1) and (ii) for Week 52 to Week 104, for those enrolled in an extended treatment duration beyond 52 weeks (Section 1.3.2).

The timing of the last randomized participant into the study (for a 52-week treatment period) will affect the timing of the Exit Visit for participants enrolled in an extended treatment duration beyond 52 weeks. As such, around the time the last participant is randomized into the study, the study team will communicate to study sites the dates for 'IP Conclusion' and 'Study Conclusion' as defined in Section 4.4. The Investigators will use these communicated dates to plan each participant's Exit Visit.

1.3.1. SoA for the First 52 Weeks

Protocol Activity	Screening Visit 0 is 3-21 days before Screening Visit 1[aa]	Screening Visit 1/Run-in is ≥2 weeks (14-21) days before Visit 2[aa]	Intervention Period and Exit Visit for the First 52 Weeks (visit window is ±7 days)														Early discontinuation /Withdrawal Visit (±7 days)	
	V0 [a]	Screening Visit 1 [a] and start of 2-wk Run-in	V2 [b]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	Exit Visit V15 [w]	Discontinue from IP Visit [c]	Withdraw from study Visit [c]
Study Week			Wk 0	Wk 4	Wk 8	Wk 12	Wk16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52		
Study Day			1	28	56	84	112	140	168	196	224	252	280	308	336	364		
Eligibility Assessments																		
Informed Consent	X																	
Reconsent [x]			←							X						→		
Genetic sample Informed Consent [d]	X																	
Hematology with differential [e]	X																	
Inclusion/Exclusion /Randomization Criteria [f]	X	X	X															
Demography/child bearing status assessment	X																	
Historical blood eosinophil counts	X [g]																	

Protocol Activity	**Screening Visit 0 is 3-21 days before Screening Visit 1[aa]**	**Screening Visit 1/Run-in is ≥2 weeks (14-21) days before Visit 2[aa]**	**Intervention Period and Exit Visit for the First 52 Weeks (visit window is ±7 days)**														**Early discontinuation /Withdrawal Visit (±7 days)**	
	V0 [a]	**Screening Visit 1 [a] and start of 2-wk Run-in**	**V2 [b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Exit Visit V15 [w]**	**Discontinue from IP Visit [c]**	**Withdraw from study Visit [c]**
Study Week			**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**		
Study Day			**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**		
Medical history including cardiovascular (CV), CV risk factors, Hepatitis B and C, COVID-19,COPD and exacerbations.		X																
Screening spirometry (including bronchodilator responsiveness testing)		X																
Parasite Screening [h]		X																
Total IgE		X																
eDiary registration and training [i]		X																
Additional Eligibility and In Study Assessments																		
Concomitant Medication Assessment [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X [k]														X [i]	X [i]	X [i]

Protocol Activity	**Screening Visit 0 is 3-21 days before Screening Visit 1[aa]**	**Screening Visit 1/Run-in is ≥2 weeks (14-21) days before Visit 2[aa]**	**Intervention Period and Exit Visit for the First 52 Weeks (visit window is ±7 days)**														**Early discontinuation /Withdrawal Visit (±7 days)**	
	V0 [a]	**Screening Visit 1 [a] and start of 2-wk Run-in**	**V2 [b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Exit Visit V15 [w]**	**Discontinue from IP Visit [c]**	**Withdraw from study Visit [c]**
Study Week			**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**		
Study Day			**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**		
Vital Signs and pulse oximetry [l]		X	X		X		X		X		X		X		X	X	X	X
ECG		X	X						X							X	X	X
mMRC		X																
Urine Pregnancy Test [m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology with differential		X [n]	X	X	X	X			X			X				X	X	X
Clinical Chemistry including liver chemistry		X	X [o]	X [o]	X [o]	X			X			X			X	X	X	X
Immunogenicity sample			X						X							X	X	X
Blood Biomarker [p]			X						X							X	X	X
Genetics sample [q]			←							X						→		
Smoking Status		X							X							X	X	X
Smoking Cessation Counselling		X														X		
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Protocol Activity	Screening Visit 0 is 3-21 days before Screening Visit 1[aa]	Screening Visit 1/Run-in is ≥2 weeks (14-21) days before Visit 2[aa]	Intervention Period and Exit Visit for the First 52 Weeks (visit window is ±7 days)														Early discontinuation /Withdrawal Visit (±7 days)	
	V0 [a]	Screening Visit 1 [a] and start of 2-wk Run-in	V2 [b]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	Exit Visit V15 [w]	Discontinue from IP Visit [c]	Withdraw from study Visit [c]
Study Week			Wk 0	Wk 4	Wk 8	Wk 12	Wk16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52		
Study Day			1	28	56	84	112	140	168	196	224	252	280	308	336	364		
Register Visit in the interactive web response system (IWRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-bronchodilator Spirometry			X						X							X	X	X
Review of eDiary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide medical problems and healthcare utilization worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Review medical problems and healthcare utilization worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Assessment r	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review COPD symptoms summary report (based on eDiary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Protocol Activity	**Screening Visit 0 is 3-21 days before Screening Visit 1[aa]**	**Screening Visit 1/Run-in is ≥2 weeks (14-21) days before Visit 2[aa]**	**Intervention Period and Exit Visit for the First 52 Weeks (visit window is ±7 days)**														**Early discontinuation /Withdrawal Visit (±7 days)**	
	V0 [a]	**Screening Visit 1 [a] and start of 2-wk Run-in**	**V2 [b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**Exit Visit V15 [w]**	**Discontinue from IP Visit [c]**	**Withdraw from study Visit [c]**
Study Week			**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**		
Study Day			**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**		
Administer Interventional Product			X [z]	X [z]	X [z]	X	X	X	X	X	X	X	X	X	X			
eDiary close out																X	X [s]	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRQoL: PRO and Health Outcomes Assessments																		
Daily Symptom Diary [t]		←	—	—	—	—	—	—	—	—	—	—	—	—	—	→		
CAT			X			X			X			X				X	X	X
SGRQ-C			X			X			X			X				X	X	X
EQ-5D-3L			X						X							X	X	X
Clinician rated response to therapy					X			X			X			X		X	X	X
Patient rated response to therapy					X			X			X			X		X	X	X
Patient global rating of COPD severity			X													X	X	X
Patient global rating of change in COPD					X			X			X			X		X	X	X

Protocol Activity	Screening Visit 0 is 3-21 days before Screening Visit 1[aa]	Screening Visit 1/Run-in is ≥2 weeks (14-21) days before Visit 2[aa]	Intervention Period and Exit Visit for the First 52 Weeks (visit window is ±7 days)														Early discontinuation /Withdrawal Visit (±7 days)	
	V0 [a]	Screening Visit 1 [a] and start of 2-wk Run-in	V2 [b]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	Exit Visit V15 [w]	Discontinue from IP Visit [c]	Withdraw from study Visit [c]
Study Week			Wk 0	Wk 4	Wk 8	Wk 12	Wk16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52		
Study Day			1	28	56	84	112	140	168	196	224	252	280	308	336	364		
Pharmacokinetics (PK) sub-study: US and China only																		
PK sub-study [u] Informed Consent	X																	
PK sample [v] (PK sub-study only)			X	X					X							X	X	X
Home healthcare for study procedures [y]						X	X	X	X	X	X	X	X	X	X			

a. Informed Consent must be obtained prior to initiating any study assessments. Screening Visit 0 must be completed and eosinophil count from the hematology test must be obtained for review prior to initiating any Screening Visit 1 assessments. **Note:** 1- For participants with a documented historical eosinophil count ≥150 cells/µL, Screening Visit 1 is performed following confirmation that Screening Visit 0 blood eosinophil count meets the inclusion criteria of ≥300 cells/µL. -2- For participants with no documented historical eosinophil count ≥150 cells/ µL, a blood sample must be collected at Visit 1 which must be >14 days after Visit 0. Refer to SRM for more details.

b. Randomization Visit 2 is ≥2 weeks after Screening Visit 1 and must be performed at least 14 days after Screening Visit 1. Results from Screening Visit 1 procedures must be available for review of randomization criteria. To be randomized, participants with no historical eosinophil count of ≥150 cells/µL in the 12 months prior to Screening Visit 0, must have an eosinophil count of ≥150 cells/µL obtained at Screening Visit 1.

c. If participant discontinues study interventional product (IP) and remains in the study, then the discontinuation from IP Visit must be conducted 4 weeks after IP discontinuation. If the participant withdraws from the study after discontinuation of IP, then the Withdraw from Study Visit is conducted within 4 weeks after the decision to withdraw from the study is made. If participant discontinues IP and withdraws from the study at the same time, a withdraw from study Visit must be conducted 4 weeks after IP discontinuation.

d. Informed Consent for optional genetics research must be obtained before collecting a sample. **China only:** Genetic Informed Consent will **not** be collected from participants in China.
e. A mandatory hematology test is performed at Screening Visit 0 and will be analyzed by the designated central laboratory. Eosinophil count must be available for review of Inclusion Criterion 2 (Section 5.1) and prior to initiating any Screening Visit 1 assessments. Participants who do not meet the eosinophil inclusion criterion of ≥ 300 cells/μL at Screening Visit 0 will be considered a screen failure.
f. Inclusion and Exclusion criteria should be assessed at Screening Visit 0 and Screening Visit 1. Randomization criteria should be assessed at Visit 2 prior to Randomization.
g. Where several historical eosinophil counts are obtainable, the highest eosinophil count should be recorded in the eCRF for each of the following specified periods: ≥1 to <6 months and 6 to12 months. In order to meet the Inclusion Criterion #2 (Section 5.1), a historical blood eosinophil measurement must meet the following: It must have been measured between 12 months and 1 month prior to Visit 0 and it must not have been measured within 14 days of a COPD exacerbation. If, in either of the 2 specified periods, the only historical documented blood eosinophil count is associated with a COPD exacerbation, then this eosinophil count cannot be used for inclusion in the study but should be recorded in the eCRF. Refer to the SRM for more information.
h. Parasitic Screening is only required in countries with high-risk or for participants who have visited high-risk countries in the past 6 months. Site staff should use local laboratories for the parasitic test.
i. Thorough eDiary training should be conducted at Screening Visit 1 and throughout the study on as-needed basis.
j. Ensure maintenance COPD medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed. 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 pre-screening/screening or receives during the study must be recorded.
k. A complete physical exam including height and weight should be conducted at Screening Visit 1. For Subsequent visits a complete physical exam including weight only should be conducted.
l. Pulse oximetry at Screening Visit 1 only
m. Pregnancy testing is only required for women of child bearing potential (WOCBP). An assessment must be made at Screening Visit 1 to determine child bearing potential of each female study participant
n. A hematology sample is only collected at Screening Visit 1 for participants with no historical eosinophil count of ≥150 cells/μL in the 12 months prior to Screening Visit 0. Note: For hematology samples collected after Randomization the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will be blinded to site staff and sponsor. However, sites will be sent total white blood counts throughout the study.
o. Participants who entered with stable chronic Hep B or Hep C, liver chemistry labs should be assessed monthly for the first 3 months (Screening Visit 1, Day 1, Week 4, Week 8, Week 12) then every 3 months (Week 24, Week 36, Week 48 and then at Week 52 (Exit Visit), or Early Withdrawal Visit); all other participants will have liver chemistry labs done every 3 months: Screening Visit 1, Day 1, Week 12, Week 24, Week 36, Week 48 and then at Week 52 (Exit Visit) or Early Withdrawal Visit
p. **China only:** Blood biomarker samples will **not** be collected from participants in China

q. The genetics sample can be collected at Visit 2 or any visit after. **China only:** Genetic blood samples will **not** be collected from participants in China.
r. As per Section 8.3.1., all AEs and SAEs will be collected from the start of study intervention (Visit 2) until the Exit Visit/Study withdrawal visit. In addition, for the Screening and Run-in Periods that occur prior to the start of study intervention, SAEs (and not AEs) related to study participation or related to any GSK product must also be collected from the point that Informed Consent is signed. **China only:** All SAEs must be collected from signing of Informed Consent.
s. For participants who continue with phone visits only.
t. The daily symptom diary will be comprised of 14 items from the EXACT instrument plus 5 additional questions on symptoms plus questions on rescue medication use and night time awakenings (Section 8.1.3.3). The symptom diary will be completed daily, in the evening, starting at Screening Visit 1 and up to Week 52. On the date of the Exit Visit, the evening diary for daily symptom reporting will not be completed.
u. Informed Consent for the optional PK sub-study (**in China and US only**) must be obtained before collecting a sample. Participation in the PK sub-study must also be recorded in the IWRS.
v. PK samples should be obtained as described in the SoA and prior to dosing on dosing days.
w. All procedures listed for Week 52 including the Exit Visit 15 apply to study participants enrolled for 52 weeks and not beyond. Importantly, no study intervention product is to be administered at Week 52 for these participants. For participants who have consented to participate in a study beyond 52 weeks, Week 52 procedures are detailed in the SoA appearing in Section 1.3.2.
x. Reconsent only applies to participants who enrolled in the study prior to Protocol Amendment 6 implementation and who have agreed to extend study participation beyond 52 weeks; these participants must re-sign a new ICF at, or prior to, completion of the Week 52 visit (**Exit Visit 15)**. Participants enrolling after Protocol Amendment 6 is in place will follow usual Informed Consent procedures to enroll in the study for up to 104 Weeks.
y. When clinic visits are impacted by restrictions imposed during the COVID-19 pandemic (e.g., quarantines, site closures, travel limitations), for participants unable to attend a site visit, home healthcare (home visits and telemedicine visits) may be used. Study procedures that can be conducted through home healthcare are those listed in the SoA table from **Visit 5** and onwards (excluding the Exit Visit), with the exception of the following procedures normally conducted in the clinic: (i) pre-bronchodilator spirometry, (ii) clinician rated response to therapy, and (iii) physical examinations (see Section 10.10.2). Consent for home healthcare can be signed at any point during the study before home healthcare is used. There is no requirement to sign consent for home healthcare if it is not needed.
z. As per Section 6.4, for the first 3 administrations of the study intervention (i.e., at Visit 2, Visit 3, and Visit 4), participants will be monitored in clinic for 1 hour after receiving the study intervention product.
aa. Under exceptional circumstances (for example, as a consequence of COVID-19-related restrictions disrupting scheduled visits), the extension of visit windows for the screening/run-in period is permissible but only with advance written permission from the GSK Medical Monitor.

1.3.2. SoA for Weeks 52 to 104

Protocol Activity	**Intervention Period and Exit Visit For Weeks 52 to 104 (visit window is ± 7 days)**														**Early discontinuation /Withdrawal Visit (±7 days)**	
	V15 [a]	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**Exit Visit V28 [b]**	**Discontinue from IP Visit [c]**	**Withdraw from study Visit [c]**
Study Week	**Wk 52 [a]**	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104**		
Study Day	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**		
Additional Eligibility and in Study Assessments																
Concomitant Medication Assessment [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination [e]	X													X	X	X
Vital Signs	X			X			X			X				X	X	X
ECG	X						X							X	X	X
Urine Pregnancy Test [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology with differential	X			X			X			X				X	X	X
Clinical Chemistry including liver chemistry	X			X [g]			X			X [g]				X	X	X
Immunogenicity sample	X						X							X	X	X
Smoking Status	X						X							X	X	X
Smoking Cessation Counselling	X													X		
Dispense Rescue medication	X	X	X	X	X	X	X	X	X	X	X	X	X			
Register Visit in IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Protocol Activity	**Intervention Period and Exit Visit For Weeks 52 to 104 (visit window is ± 7 days)**														**Early discontinuation /Withdrawal Visit (±7 days)**	
	V15 [a]	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**Exit Visit V28 [b]**	**Discontinue from IP Visit [c]**	**Withdraw from study Visit [c]**
Study Week	**Wk 52 [a]**	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104**		
Study Day	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**		
Pre-bronchodilator Spirometry	X						X							X	X	X
Review of eDiary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide medical problems and healthcare utilization worksheet	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Review medical problems and healthcare utilization worksheet	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review COPD symptoms summary report (based on eDiary)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer Interventional Product	X	X	X	X	X	X	X	X	X	X	X	X	X			
eDiary close out														X	X [h]	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRQoL: PRO and Health Outcomes Assessments																
Daily Symptom Diary [i]	◄							X						►		
CAT	X						X							X	X	X
SGRQ-C	X						X							X	X	X

Protocol Activity	**Intervention Period and Exit Visit For Weeks 52 to 104 (visit window is ± 7 days)**														**Early discontinuation /Withdrawal Visit (±7 days)**	
	V15 [a]	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**Exit Visit V28 [b]**	**Discontinue from IP Visit [c]**	**Withdraw from study Visit [c]**
Study Week	**Wk 52 [a]**	**Wk 56**	**Wk 60**	**Wk 64**	**Wk 68**	**Wk 72**	**Wk 76**	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104**		
Study Day	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**		
EQ-5D-3L	X						X							X	X	X
Clinician rated response to therapy	X			X			X			X				X	X	X
Patient rated response to therapy	X			X			X			X				X	X	X
Patient global rating of COPD severity	X													X	X	X
Patient global rating of change in COPD	X			X			X			X				X	X	X
Home healthcare for study procedures [j]	X	X	X	X	X	X	X	X	X	X	X	X	X			

a. Procedures listed for V15 at Week 52 only apply to study participants receiving treatment beyond 52 weeks (i.e., Week 52 to a maximum of Week 104). For these participants, a dose of intervention product must be taken at Week 52.

b. Exit visit will be either at Week 104 or at a **scheduled visit** closest to the date (i.e., on or immediately before, but not after) the last randomized participant is scheduled to complete their Exit Visit at Week 52 (as per the SoA in Section 1.3.1), whichever is sooner. In the instance that the Exit Visit occurs sooner than Week 104, all predefined Exit Visit assessments are to be conducted in lieu of the predefined assessments for a scheduled visit. Importantly, the Exit Visit should occur 4 weeks after the last dose of study intervention product and no study intervention product is to be administered at the Exit Visit.

c. If a participant discontinues study interventional product and remains in the study, then the discontinuation from IP Visit must be conducted 4 weeks after IP discontinuation. If the participant withdraws from the study after discontinuation of IP, then the Withdraw from Study Visit is conducted within 4 weeks after the study withdrawal decision is made. If a participant discontinues IP and withdraws from the study at the same time, a withdraw from study Visit must be conducted 4 weeks after IP discontinuation.

d. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving during the study must be recorded.

Protocol Activity	Intervention Period and Exit Visit For Weeks 52 to 104 (visit window is ± 7 days)														Early discontinuation /Withdrawal Visit (±7 days)	
	V15 [a]	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	Exit Visit V28 [b]	Discontinue from IP Visit [c]	Withdraw from study Visit [c]
Study Week	Wk 52 [a]	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Wk 104		
Study Day	364	392	420	448	476	504	532	560	588	616	644	672	700	728		

e. A complete physical exam including weight should be conducted.
f. Pregnancy testing is only required for women of child bearing potential (WOCBP).
g. Week 64 and Week 88 measurements **do not apply** to study participants who **do not have** stable chronic Hep B or Hep C. For those with stable chronic Hep B or Hep C, collections to be made every 3 months (Weeks 52, 64, 76, 88, 100, and the Exit Visit at Week 104). For all others, collections to be made every 6 months (Weeks 52, 76, 100, and the Exit Visit at Week 104).
h. For participants who continue with phone visits only.
i. From Week 52 to Week 104, the daily symptom diary will be comprised of 3 items from the EXACT instrument (not all 14 items) plus 5 additional questions on symptoms plus questions on rescue medication use and night time awakenings (Section 8.1.3.3). The symptom diary will be completed daily, in the evening, throughout the treatment period. At the Exit Visit, the evening diary for daily symptom reporting will not be completed.
j. When clinic visits are impacted by restrictions imposed during the COVID-19 pandemic (e.g., quarantines, site closures, travel limitations), for participants unable to attend a site visit, home healthcare (home visits and telemedicine visits) may be used. Study procedures that can be conducted through home healthcare are those listed in the SoA table from V15 onwards (excluding the Exit Visit), with the exception of the following procedures normally conducted in the clinic: (i) pre-bronchodilator spirometry, (ii) clinician rated response to therapy, and (iii) physical examinations (see Section 10.10.2). Consent for home healthcare can be signed at any point during the study before home healthcare is used. There is no requirement to sign consent for home healthcare if it is not needed.

2. INTRODUCTION

2.1. Study Rationale

While chronic obstructive pulmonary disease (COPD) is generally viewed as a disease driven by neutrophilic inflammation, up to 40% of COPD patients have an inflammatory pattern that includes elevated sputum eosinophils [Brightling, 2005; Saha, 2006]. In severe COPD patients, sputum eosinophils and Interleukin (IL)-5 levels are elevated to similar levels as those seen in severe asthmatics [Bafadhel, 2012a]. Notably, COPD patients with eosinophilic inflammation cannot be distinguished based on clinical features and lung function alone from those without eosinophilic inflammation [Saha, 2006]. Furthermore, increased eosinophilic inflammation in COPD has been associated with increased risk of exacerbations [Vedel-Krogh, 2016]. COPD exacerbations are characterized by periods of acute worsening of symptoms, deterioration in lung function, and decreased health-related quality of life (HRQoL) [Vogelmeier, 2017] and potentially contribute to further permanent decrements in lung function. Recent studies identified that increased eosinophilic airway inflammation occurred during COPD exacerbations [Bafadhel, 2011] and that peripheral eosinophils levels in the blood were used successfully as a surrogate marker to predict response to corticosteroid therapy [Bafadhel, 2012b; Bafadhel, 2017]. A study by Siva et al [Siva, 2007] showed that a treatment strategy that aimed to reduce sputum eosinophils in COPD showed a significant reduction in severe exacerbations compared to a treatment strategy aimed towards symptom reductions alone.

Based on the observation that airway eosinophilic inflammation is associated with COPD exacerbations [Bafadhel, 2011; Bafadhel, 2017], that a treatment regimen designed to reduce eosinophils will attenuate COPD exacerbations, and that airway levels of IL-5 and eosinophils are comparable in both severe eosinophilic asthma and in eosinophilic-phenotype of COPD, the mepolizumab COPD program was designed to study a COPD patient population meeting a blood eosinophil threshold with a history of exacerbations despite receiving inhaled corticosteroid (ICS)-based triple maintenance therapy. This clinical experience and the successful reduction of acute exacerbation of COPD (AECOPD) by IL-5 inhibition with mepolizumab [Pavord, 2017] suggests that the management of exacerbations can be tailored by therapy directed at a treatable trait.

Mepolizumab is a humanised immunoglobulin G (IgG) antibody (IgG1, kappa) which binds to and inhibits the ability of IL-5 to bind to the IL-5 receptor. IL-5 receptors are primarily expressed on eosinophils. IL-5 is a major regulator of eosinophils and upon binding to the IL-5 receptor results in accumulation in tissues and modulation of eosinophil behaviour from maturation to survival. Mepolizumab can reduce eosinophils in the periphery and in tissues.

Two 52-week, randomized, placebo-controlled, double-blind, parallel-group, multi-center initial Phase IIIA studies, MEA117106 and MEA117113, evaluated the effect of mepolizumab, administered every 4 weeks through subcutaneous (SC) injection, on the rate of moderate/severe COPD exacerbations in participants with a history of COPD exacerbations despite receiving ICS-based triple maintenance therapy [Pavord, 2017]. Studies MEA117106 and MEA117113 demonstrated that treatment with mepolizumab

led to improvements in exacerbations and other efficacy endpoints when compared with placebo. In addition, in these studies, the safety profile of mepolizumab was similar to placebo and no new safety concerns were identified in this COPD patient population to those identified in the severe asthma program.

The results from MEA117113 and MEA117106 demonstrate that while patients selected with an exacerbating phenotype and with a blood eosinophil count ≥150 cells/µL at Screening or ≥300 cells/µL in previous 12 months achieved a clinically relevant reduction in moderate/severe exacerbations, patients with a blood eosinophil count ≥300 cells/µL (in previous 12 months or at Screening) are more likely to achieve greater benefit from mepolizumab. Thus, a blood eosinophil count ≥300 cells/µL provides a clear threshold to identify patients that are more likely to benefit from mepolizumab. In this study, to ensure stability of eosinophil counts, an additional requirement is for a documented historical eosinophil count of ≥150 cells/µL in the 12 months prior to Screening Visit 0. Participants with no documented historical eosinophil count of ≥150 cells/µL must meet this threshold at the Screening Visit 1 assessment prior to randomization.

Therefore, this study will provide additional efficacy data on the benefits of mepolizumab treatment in a more refined patient population expected to benefit from treatment. In addition to exacerbation data, this study will provide additional important HRQoL data for mepolizumab compared with placebo.

2.2. Background

COPD is a chronic progressive disease with rising morbidity and mortality and is currently the fourth leading cause of death in the world [WHO Report, 2008]; Lozano, 2012]. The disease course is marked by progressive deterioration in airflow and increase in AECOPD frequency that contribute to the overall disease severity [Vogelmeier, 2017]. In addition, a study by [Hurst, 2010] showed that the single best predictor of exacerbations was previous exacerbations.

AECOPD are heterogeneous in nature with respect to their inflammatory component. A study by Siva et al [Siva, 2007] showed that a treatment strategy that aimed to reduce sputum eosinophil counts in COPD showed a significant reduction in severe exacerbations compared with a treatment strategy aimed towards optimizing symptoms alone. Subsequent studies found that increased eosinophilic airway inflammation occurred during COPD exacerbations [Bafadhel, 2011] and that blood eosinophil levels were used successfully as a surrogate for sputum eosinophil levels to predict response to corticosteroid therapy [Bafadhel, 2017]. Furthermore, the 2019 GOLD report recommends the use of blood eosinophil count as a biomarker for considering treatment of COPD with inhaled corticosteroids [GOLD, 2019]. Additionally, the results from the mepolizumab COPD initial phase IIIA studies indicate that blood eosinophil levels are a useful biomarker to tailor treatment and prevent exacerbations for those COPD patients with an eosinophilic phenotype defined by the level of blood eosinophil counts [Pavord, 2017].

The [GOLD, 2019] report advocates the use of one or more long-acting inhaled bronchodilators (long acting beta2 -agonist [LABA]) or (long acting muscarinic antagonist [LAMA]) in addition to ICS for patients with more advanced disease, high blood eosinophil count and high risk of exacerbations [GOLD, 2019]

The concurrent use of these medications (i.e., ICS plus LABA plus LAMA) is often termed 'triple inhaled maintenance therapy' and is usually considered optimal for COPD patients at risk of exacerbations. For patients who continue to exacerbate despite the use of triple inhaled therapy (approximately 40% of patients on inhaled triple therapy), there are limited additional maintenance treatment options. Of these patients, approximately 20% have eosinophil levels ≥300 cells/µL [Müllerova, 2017].

Overall, there are approximately 6.1% of COPD patients who have progressive disease that is not controlled with triple therapy, and blood eosinophil levels ≥300 cells/µL, who could benefit from the attenuation of eosinophilic inflammation by mepolizumab [Benson, 2018].

This population of patients is at higher risk of poor outcomes including a 2-fold increased risk of moderate/severe exacerbations and a 26% increase in mortality compared with the general COPD population [GlaxoSmithKline document number 2017N350371_00].

The mepolizumab COPD program addresses a key unmet need in patients at high risk for adverse outcomes. The patient population for mepolizumab includes patients who continue to experience AECOPD despite optimized COPD therapy namely ICS-based triple inhaled maintenance therapy (see inclusion criteria Section 5.1). There are limited or no additional therapeutic options [GOLD, 2019] for this target population with a high burden of disease despite intensive therapy.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of mepolizumab may be found in the current version of the Investigator's Brochure (IB).

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Mepolizumab		
Risk of Systemic Reactions (Allergic [type I hypersensitivity] and Other systemic), including Anaphylaxis	In the integrated initial Phase IIIA COPD trials MEA117106 and MEA117113, the incidence of systemic reactions was 2% in the mepolizumab All Doses group and 2% in the placebo group. Systemic reactions reported to date across the mepolizumab programme are summarised in the Investigator Brochure (IB) "Safety in Clinical studies" section under each indication studied and in Section 6 of the IB titled 'Summary of Data and Guidance for the Investigator'	Regular monitoring of serious adverse events (SAEs) by Medical Monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GlaxoSmithKline (GSK) study team and/or safety review team. Customized AE and SAE case report form (CRF) utilized for 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 2) Participants are monitored in clinic for 1 hour after the first 3 administrations of study treatment and then according to monitoring policies for the center.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
		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.
Local Injection site reactions	In the integrated Phase IIIA COPD trials MEA117106 and MEA117113, incidence of local injection site reactions was 3% in the mepolizumab All Doses group and 3% in the placebo group. Local injection site reactions reported to date across the mepolizumab program are summarized in the IB "Safety in Clinical studies" section under each indication studied and in Section 6 titled 'Summary of Data and Guidance for the Investigator'	Regular monitoring of SAEs by Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or safety review team. Customised AE and SAE case report form (CRF) utilised for collection of information for local injection site reaction adverse events.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Potential risk of immunogenicity	Mepolizumab has low immunogenic potential. Overall, the immunogenicity results from clinical studies across the mepolizumab program demonstrate that the presence of anti-drug antibodies (ADAs) is not associated with any specific adverse events, anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics (PK) or pharmacodynamics (PD) of mepolizumab in the majority of participants and there was no evidence of a correlation between antibody titers and change in eosinophil level. Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; See Section 5.4 'Clinical Immunogenicity' and in Section 6 'Summary of Data and guidance for the investigator".	Blood samples will be collected for detection of both ADA and neutralizing antibodies (Nab).
Potential risk for adverse cardiovascular (CV) effects	In the integrated Phase IIIA COPD trials 117106 and 117113, incidence of Investigator reported serious cardiac, vascular and thromboembolic events was 5% in the mepolizumab All Doses group	Regular monitoring of SAE by Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK study team and/or safety review team.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	and 4% in the placebo group. The incidence of fatal and non-fatal serious adverse events adjudicated by the external independent Clinical End Point committee (CEC) in a blinded fashion to the CV category was 4% across all treatment groups. Cardiac events reported to date across the mepolizumab programme are summarised in the IB "Safety in Clinical studies" section under each indication studied.	Electrocardiography (ECG) monitoring during the trial; As per GSK standard practice use of standardized CRFs to collect additional data on protocol-specified CV events (i.e., myocardial infarction, hospitalization for unstable angina and congestive heart failure, arterial thrombosis, pulmonary embolism and deep vein thrombosis); MACE events and all SAE reports will be adjudicated by external independent CEC in a blinded fashion.
Potential risk for increase in infections - theoretical concern with biologics	In the integrated Phase IIIA COPD trials 117106 and 117113, incidence of events in the Infections and Infestation System Organ Class (SOC) was 51% in the mepolizumab All Doses group and 53% in the placebo group. The incidence of events potentially representing opportunistic infections was 3% in the mepolizumab groups and 2% in placebo group. There were no parasitic infections reported in these studies. Infections reported to date across the mepolizumab development	Regular monitoring of SAE by Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK study team and/or safety review team Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are also excluded

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	program are summarized in the IB "Safety in Clinical studies" section under each indication studied, and in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	
Potential risk for increase in malignancies - theoretical concern with biologics	In the integrated initial Phase IIIA COPD trials 117106 and 117113, incidence of malignancy was 2% in the mepolizumab All Doses group and 2% in placebo group. Malignancies reported to date across the mepolizumab development program are summarized in the IB "Safety in Clinical studies" section under each indication studied.	Regular monitoring of SAE by Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK study team/safety review team
Study Procedures		
Blinding eosinophil counts	This study is a double-blind study which may be used to support approval for the use of mepolizumab in the reduction of moderate/severe COPD exacerbations. Unblinded eosinophil counts after the first administration of IP may compromise the integrity of the study.	Patients will be seen monthly by Investigators (or delegate). After Randomization, neither the site staff nor GSK personnel will be sent results from the central laboratory for: absolute and differential values for eosinophils, lymphocytes, basophils, neutrophils and monocytes. However, sites will be sent

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
		total white blood counts throughout the study.

2.3.2. Benefit Assessment

Study 208657 will investigate the efficacy and safety of mepolizumab in the reduction of moderate/severe COPD exacerbations in participants receiving intensive therapeutic intervention for COPD treatment recommended for this population with severe disease and high risk of AECOPD.

Exacerbations are a major concern to COPD patients and lead to a worsening of the quality of life for patients. A reduction in frequency of moderate and severe exacerbations may improve a patient's quality of life and may reduce hospitalizations.

Participants in this study will be followed-up monthly and will continue optimized maintenance COPD therapy and therefore may benefit both from the additional assurance of medicine compliance and monitoring of their current maintenance therapy. Participants may also benefit from regular monitoring of their COPD symptoms and potential identification of exacerbations.

Data obtained from this study will provide additional evaluation of the efficacy and safety of mepolizumab delivered as a pre-filled liquid formulation in a safety syringe.

2.3.3. Overall Benefit: Risk Conclusion

Data from mepolizumab preclinical and clinical development demonstrate the ability of mepolizumab to inhibit IL-5, and consequently treat inflammatory conditions linked to an eosinophil signal, such as COPD patients predisposed to future exacerbations. To date, the safety profile of mepolizumab has been favourable. Furthermore, preclinical and clinical data to date have not identified any safety concerns that would preclude further investigation in COPD. Importantly, in addition to their randomized IP, all participants will be receiving optimized maintenance COPD therapy throughout the study. Therefore, further investigation of the efficacy and safety of mepolizumab is justified in study 208657.

3. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary • To evaluate the efficacy of mepolizumab 100 mg subcutaneous (SC) compared to placebo, given every 4 weeks in liquid formulation by safety syringe (SS) to COPD participants at high risk of exacerbations despite the use of optimized COPD maintenance therapy.	• Annualized rate of moderate/severe exacerbations
Secondary • To evaluate mepolizumab 100 mg SC compared to placebo given every 4 weeks	• Time to first moderate/severe exacerbation

Objective	Endpoint
in liquid formulation by SS on additional efficacy assessments, health related quality of life (HRQoL), health care utilization, and symptoms	• Proportion of COPD assessment test (CAT) responders (≥2 unit reduction in CAT score from baseline) at Week 52 • Proportion of St. George's Respiratory Questionnaire (SGRQ) total score responders (measured using the St. George's Respiratory Questionnaire for COPD [SGRQ-C], and defined as ≥4 point reduction in SGRQ total score from Baseline) at Week 52 • Proportion of Evaluating Respiratory Symptoms in COPD (E-RS: COPD) responders (≥2 unit reduction in total score from Baseline) at Week 52 • Annualized rate of exacerbations requiring Emergency Department (ED) visit and/or hospitalization
Other • To further investigate other endpoints	CCI [redacted] • Change from Baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) • CAT responders at Week 24 • CAT change from baseline at Week 24 and 52 • SGRQ responders at Week 24 • SGRQ change from Baseline at Week 24 and 52

Objective	Endpoint
	• Proportion of Evaluating Respiratory Symptoms in COPD (E-RS: COPD) responders at Week 24 • Proportion of E-RS: COPD responders: sub-scales of breathlessness, cough and sputum and chest symptoms at Week 24 and 52 • Change from Baseline in E-RS: COPD Total Score at Week 24 and 52 • CCI [redacted]
CCI [redacted]	
Safety Objective • To evaluate the safety of mepolizumab in participants with COPD	• Incidence of AEs/SAEs including systemic reactions. • Incidence of adjudicated SAE reports and MACE events (CV death, non-fatal myocardial infarction, and non-fatal stroke) • Vital signs including blood pressure (BP), body temperature, pulse rate • ECG assessments • Mortality (all cause including respiratory and cardiovascular causes of death) • Presence of anti-drug antibodies (ADA) to mepolizumab • Hematological and clinical chemistry parameters
Health Outcome Endpoints • To further evaluate the effect of mepolizumab 100 mg SC on health care utilization.	• Healthcare utilization for COPD including hospitalization, ED, and physician office/clinic visits

3.1. Pharmacokinetics Sub-study: China and US only

Objective	Endpoint
• To evaluate the PK of mepolizumab 100 mg in liquid formulation administered subcutaneously by SS in Chinese participants and to assess potential PK ethnic differences between non-Asian participants in the US and Chinese participants in China	• Plasma mepolizumab concentrations

4. STUDY DESIGN

4.1. Overall Design

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities (SoA, Section 1.3), are essential and required for study conduct.

This is a multi-center, randomized, placebo-controlled, double-blind, parallel group, trial evaluating mepolizumab 100 mg compared with placebo given every 4 weeks through SC injection of a liquid formulation delivered in a pre-filled safety syringe.

It is estimated that approximately 4000 participants will be screened to achieve a target global randomization of approximately 800 randomized participants. The number of randomized participants may increase up to approximately 1400 following blinded sample size re-evaluation (Section 9.2). Eligible participants will be randomized 1:1 to mepolizumab 100 mg or placebo.

During Screening Visit 0, a mandatory haematology blood sample is collected. The Investigator or designee must review the results of the Visit 0 blood eosinophil count prior to initiating Screening Visit 1. Participants with eosinophil count less than 300 cells/μL cannot proceed to Screening Visit 1 and will be considered a screen failure. Participants must also have a documented historical eosinophil count of ≥150/μL in the 12 months prior to Screening Visit 0 and the historical eosinophil count must not have been measured during a COPD exacerbation. Participants with no documented historical eosinophil count of ≥150 cells/μL must meet this threshold based on the Screening Visit 1 assessment in order to return for Visit 2 (Inclusion Criteria, Section 5.1).

Investigators are required to thoroughly review participants' medical records to identify historical eosinophil counts. It is only in the absence of documented records will eosinophils measurement at Screening Visit1 be considered.

Participants who meet all the inclusion criteria and none of the exclusion criteria at Screening Visit 0 and Screening Visit 1 will enter a 2-week Run-in period. Excluding screening and run-in periods, study participants will remain in the study for at least

52 weeks (see SoA in Section 1.3.1) and up to a maximum of 104 weeks (See SoA in Section 1.3.2). More specifically,

- For participants enrolled for 52 weeks (SoA in Section 1.3.1), their Exit Visit will occur at Week 52, 4 weeks after the last scheduled dose of IP.

- For participants enrolled beyond 52 weeks (SoA in Section 1.3.2), their Exit Visit will be at Week 104 or until a scheduled visit that aligns to the date (i.e., that occurs on or before) the last randomized participant is scheduled to complete their Week 52 Exit Visit, whichever is sooner. The Exit Visit will occur 4 weeks after the last dose of IP.

The timing of the last randomized participant into the study will affect the timing of the Exit Visit for participants enrolled beyond 52 weeks. All participants will be expected to complete at least 52 weeks of the study. The last randomized participant will be scheduled to complete only 52 weeks of the study. See Section 4.4 for additional details.

In addition to the blood eosinophil inclusion criteria, participants must also have a history of regular maintenance use of ICS-based triple COPD standard of care treatment (as further defined in inclusion criteria Section 5.1) for at least 12 months prior to Screening Visit 1. In addition, for at least 3 months immediately prior to Screening Visit 1, each participant must have a recorded history of use of an ICS-based inhaled triple regimen (ICS plus LABA plus LAMA) with a minimum inhaled corticosteroid at a dose of ≥500 mcg/day fluticasone propionate or equivalent. A detailed schematic is provided in the study reference manual (SRM) giving examples of ICS plus LABA plus LAMA therapy in the 12 months prior to Screening Visit 1.

Participants are also required to have a history of at least 2 moderate COPD exacerbations that were treated with systemic corticosteroids (intramuscular (IM), intravenous, or oral) with or without antibiotics, or 1 severe exacerbation requiring hospitalization in the 12 months prior to Screening Visit 1 and one exacerbation must have occurred while the participant was receiving ICS plus LABA plus LAMA (Inclusion Criteria, Section 5.1). All participants will receive optimized maintenance COPD therapy throughout the entire duration of the study regardless of treatment arm assignment. In addition to ICS plus LABA plus LAMA, participants can enter the study with other COPD maintenance medications.

The requirement for ICS plus LABA plus LAMA is predicated on the participant's tolerance and safety to ICS and to long-acting inhaled bronchodilators. However, it is recognized that maximal tolerated and safe therapy may not allow the use of a LAMA or LABA in combination with ICS in a given participant. Where documentation of safety and tolerance does not allow the use of LABA or LAMA, participants will be allowed into the study on ICS plus LABA or ICS plus LAMA. These circumstances must be reviewed and discussed with the Medical Monitor.

It is also recognized that escalation or de-escalation of COPD maintenance medications may need to be individualized if clinically crucial for a participant. The investigator will

discuss all cases with the Medical Monitor before initiating changes to a participant's COPD maintenance medication regimen.

The study interventional product, prepared in a pre-filled safety syringe, will be administered as a single SC injection given every 4 weeks at every study visit (except for the Exit Visit), beginning at the Randomization Visit (Visit 2). The Exit Visit will occur 4 weeks after the last administration of intervention product. The primary efficacy endpoint will include exacerbations reported after the first dose up to and including the Exit Visit.

Participants should understand and agree to complete an electronic diary (eDiary) throughout the study to be considered eligible. The daily eDiary consists of questions to be answered each evening before bedtime. The same eDiary will be used to capture patient reported outcomes (PROs) (see Section 8.1.3). Site staff must therefore train participants on the proper use of the eDiary and completion of PROs at Visit 1. Compliance with completion of the daily eDiary will be captured during the Run-in period and throughout the study. Participants must meet the eDiary compliance requirement for them to be eligible for randomization.

Instream review of the eDiary data will monitor participant symptoms suggestive of an exacerbation and will also trigger prompts to encourage site staff to contact the patient for assessment and possible diagnosis of AECOPD.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SRM. The SRM will provide the site staff with administrative and detailed technical information that does not impact participant safety.

Note: The COVID-19 pandemic has impacted the conduct of this clinical study. Where applicable country and local regulations and infrastructure allow, and at the discretion of Investigator and consent of the participant, home healthcare may take place at a location other than the clinical study site, e.g., the participant's home to perform study assessments. Refer to Appendix 10 and the SRM for details on COVID-19 pandemic measures and home healthcare for study assessments.

Pharmacokinetic Sub-study: China and US only

An optional pharmacokinetic (PK) sub-study will be included in China and the US to assess potential ethnic differences in the PK of mepolizumab 100 mg, in liquid formulation, between non-Asian participants in the US and Chinese participants in China. PK blood samples will be collected from approximately 50 randomized participants from the US and approximately 50 randomized participants from China to ensure at least 20 participants from each country provide PK information related to mepolizumab. This PK assessment will be conducted over the first 52 weeks of the study period only.

4.2. Scientific Rationale for Study Design

This study is designed to evaluate the efficacy and safety of mepolizumab 100 mg SC over a treatment period of at least 52 weeks and up to 104 weeks, in participants who exacerbate despite regular use of optimal therapy appropriate for severe COPD patients,

in the 12 months prior to Screening Visit 1. Optimized standard of care (SoC) therapy must include a well-documented requirement for ICS-based triple COPD maintenance treatment (per inclusion criteria Section 5.1) for at least 12 months prior to Screening Visit 1. Participants are also required to have a history of at least 2 moderate COPD exacerbations that were treated with systemic corticosteroid (intramuscular (IM), intravenous, or oral) with or without antibiotics, or 1 severe exacerbation requiring hospitalization in the 12 months prior to Screening Visit 1.

All participants will receive optimized maintenance COPD therapy throughout the entire duration of the study regardless of intervention arm assignment.

The 2-week Run-in period allows for the assessment of participant understanding and compliance with the daily eDiary to establish Baseline E-RS: COPD symptoms, and to allow adequate time for receipt of results from assessments collected at Screening Visit 1.

A Screening blood eosinophil count threshold of ≥300 cells/µL at Screening Visit 0 has been selected since the mepolizumab initial phase IIIA studies have shown that patients with an eosinophil count ≥300 cells/µL are likely to achieve greater benefit from mepolizumab treatment.

For participants with no documented historical eosinophil count of ≥150 cells/µL in the 12 months prior Screening Visit 0, the greater than 14 day period between Screening Visit 0 and Screening Visit 1 allows for a repeated eosinophil count measurement at Screening Visit 1.

The protocol objective is to collect data over the full study period, whether participants continue on IP or in the case of premature discontinuation from IP. However, the decision to continue in the study after premature discontinuation from IP remains the prerogative of the participant. Participants who agree to continue in the study after premature discontinuation from IP (for any reason) will continue to be contacted by the study site, either through in clinic visits or by phone as agreed with the participant, on a monthly basis (aligned to their study schedule) until the end of their planned participation, to enable capture of post-intervention information.

4.3. Justification of Dose

Evidence from the two initial phase IIIA studies demonstrated that in individuals with blood eosinophils ≥150 cells/µL at screening or ≥300 cells/µL in the prior year, a 100 mg SC dose provided a clinically relevant reduction in the primary endpoint of moderate/severe exacerbations of 18 to 20% compared with placebo. This magnitude of reduction was consistent across studies (MEA117113 and MEA117106 High Stratum) and across the two doses investigated with an 18-20% reduction with 100 mg and 14% reduction with 300 mg [Pavord, 2017]. The absence of evidence of a greater reduction in the rate of moderate/severe exacerbations and prolonged time to first moderate/severe exacerbation with 300 mg SC, as well as the absence of evidence of an exposure-response for those endpoints, support the rationale for a 100 mg SC therapeutic dose administered every 4 weeks in patients with COPD [Pavord, 2017].

Furthermore, the safety profile following mepolizumab treatment was comparable to placebo, irrespective of dose. From the well-characterized blood eosinophil dose-response established across multiple eosinophilic conditions, this dose represents approximately the dose providing the ID90 for blood eosinophil reduction.

4.4. End of Study Definition

The timing of the last randomized participant into the study will affect the timing of the Exit Visit for participants enrolled in an extended treatment duration beyond 52 weeks. As such, around the time the last participant is randomized into the study, the study team will communicate to study sites the dates for 'IP Conclusion' and 'Study Conclusion' as defined below. The Investigators will use these communicated dates to plan each participant's Exit Visit.

4.4.1. Participants Enrolled for 52 Weeks

Completion of Intervention Period: A participant will be considered to have completed the study intervention period if he/she continues to receive IP up to and including the last scheduled IP dose at Week 48.

Completion of Study: A participant will be considered to have completed the study if he/she continues to participate in the study until the scheduled Week 52 Exit Visit, regardless of whether the participant continued to receive IP during the treatment period.

4.4.2. Participants Enrolled Beyond 52 Weeks

Completion of Intervention Period: Whichever of the following [(i) or (ii)] is sooner, a participant will be considered to have completed the study intervention period if he/she:

(i) Continues to receive IP up to and including the last scheduled IP dose at Week 100.

OR

(ii) Continues to receive IP until a **scheduled visit** that aligns to the date the last randomized participant is scheduled to receive the last dose of IP at Week 48 (hereafter referred to as the **'IP Conclusion' date**). In this scenario, a participant will have completed the study intervention period if he/she continues to receive IP up to and including the **scheduled visit** that occurs **on or immediately before** the 'IP Conclusion' date.

Completion of Study: Whichever of the following is sooner [(i) or (ii)] and regardless of whether the participant continued to receive IP during the treatment period, a participant will be considered to have completed the study if he/she:

(i) Continues to participate in the study until the scheduled Exit Visit at Week 104.

OR

(ii) Continues to participate in the study until a **scheduled visit** that aligns to the date the last randomized participant is scheduled to complete the Week 52 Exit Visit (hereafter referred to as the **'Study Conclusion' date**). In this scenario, a participant will have completed the study if the participant continued in the study until a **scheduled visit** that occurs **on or immediately before** the 'Study Conclusion' date.

4.4.3. End of Study

The end of the study is defined as the date of the last scheduled visit, shown in the SoA for 52 weeks (Section 1.3.1.), for the last participant in the trial globally.

5. STUDY POPULATION

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the below criteria apply. Further details pertaining to the Inclusion Criteria can be found in the SRM.

Age

1. Participant must be at least 40 years of age at Screening Visit 1

Blood eosinophils

2. A peripheral blood eosinophil count of ≥300 cells/µL from the hematology sample collected at Screening Visit 0

AND

A documented historical blood eosinophil count of ≥150/µL in the 12 months prior to Screening Visit 0 that meets the following: It must have been measured between 12 months and 1 month prior to Visit 0, and it must not have been measured within 14 days of a COPD exacerbation.

Participants with no documented historical blood eosinophil count of ≥150 cells/µL must meet this threshold based on the Screening Visit 1 assessment in order to return for Randomization Visit 2.

Type of Participant and Disease Characteristics

3. **COPD Diagnosis:** Participants with a clinically documented history of COPD for at least 1 year in accordance with the definition by the American Thoracic Society/European Respiratory Society [Celli, 2004]

4. **Severity of COPD:** Participants must present with the following:

- A measured pre- and post-salbutamol FEV_1/FVC ratio of <0.70 at Screening Visit 1 to confirm the diagnosis of COPD

- A measured post-salbutamol FEV_1>20% and ≤80% of predicted normal values calculated using NHANES III reference equations [Hankinson, 1999; Hankinson, 2010] at Screening Visit 1.

5. **History of Exacerbations:** Participants must have a well-documented history (e.g., medical record verification) in the 12 months prior to Screening Visit 1 of:

   - Two or more moderate COPD exacerbations that were treated with systemic corticosteroids (intramuscular (IM), intravenous, or oral) with or without antibiotics

   OR

   - At least one severe COPD exacerbation requiring hospitalization

   Note: At least one exacerbation must have occurred while the participant was taking inhaled triple therapy, ICS plus LABA plus LAMA unless documented intolerance or safety risk with either of the two long-acting bronchodilators. If intolerance is documented, ICS plus LABA or ICS plus LAMA would be allowable after discussion with the Medical Monitor.

   Note: COPD exacerbation(s) related to laboratory confirmed COVID-19 infection must not be counted as COPD exacerbation(s) for inclusion in the study.

6. **Concomitant COPD therapy**: Participants must have a well-documented requirement for optimized standard of care background therapy that includes ICS plus 2 additional COPD medications (i.e., ICS-based triple therapy) for the 12 months prior to Screening Visit 1 and meets the following criteria:

   - Immediately prior to Screening Visit 1, minimum of 3 months of use of an **a)** inhaled corticosteroid at a dose ≥500 mcg/day fluticasone propionate dose equivalent plus **b)** LABA and **c)** LAMA unless documentation of safety or intolerance issues related to LABA or LAMA.
   - For participants who **are not** continually maintained on ICS plus LABA plus LAMA for the entire 12 months prior to Visit 1 use of the following is allowed (but not in the 3 months immediately prior to Visit 1):
     a. inhaled corticosteroid at a dose ≥500 mcg/day fluticasone propionate dose equivalent **plus**
     b. inhaled LABA or inhaled LAMA **and**
     c. Phosphodiesterase-4-inhibitors, methylxanthines, or scheduled daily use of short acting $beta_2$-agonist (SABA) and/or short acting muscarinic antagonist (SAMA).

   Note: Where intolerance or safety risk is documented for either LAMA or LABA, ICS-based inhaled dual maintenance therapy, either ICS plus LABA or ICS plus LAMA, is allowed in the 12 months prior to Visit 1 and during the clinical trial but must be discussed with the Medical Monitor.

   Note: Participants must be willing to receive optimized maintenance COPD therapy for the duration of the study.

7. **Smoking Status:** Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years at Screening (Visit 1) [number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Screening Visit 1.

   Note: Pipe and/or cigar use cannot be used to calculate pack-year history.

Sex

8. **Male or female:** Contraceptive use for 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 5, during the intervention period and for at least 16 weeks after the last dose of study intervention. The principal investigator (PI) should evaluate the effectiveness of the contraceptive method in relation to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy urine test within 24 hours before the first dose of study intervention.

  If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

  Additional requirements for pregnancy testing during and after study intervention are located in Appendix 5

- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk of inclusion of a woman with an early undetected pregnancy

Informed Consent

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

Other

French participants: In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

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

Medical Conditions

1. **Asthma:** Participants with a past history or concurrent diagnosis of asthma are excluded regardless of whether they have active or inactive disease.

2. **Other respiratory disorders**: The Investigator must judge that COPD is the primary diagnosis accounting for the clinical manifestations of the lung disease. Participants with α1-antitrypsin deficiency as the underlying cause of COPD are excluded. Also, excluded are participants with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases.
3. **COPD stability**: Participants with pneumonia, COPD exacerbation, or lower respiratory tract infection within the 4 weeks prior to Screening Visit 1.
4. **Lung resection**: Participants with lung volume reduction surgery within the 12 months prior to Screening Visit 1.
5. **Pulmonary rehabilitation program**: Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening Visit 1. Participants who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
6. **Oxygen:** Participants receiving treatment with oxygen more than 2 L/min at rest over 24 hrs. For Participants receiving oxygen treatment, participants should demonstrate an oxyhemoglobin saturation greater than or equal to 89% while breathing supplemental oxygen.
7. **12-lead ECG at Screening Visit 1**: Participants with a QT interval, from the ECG conducted at Screening Visit 1, corrected with Fridericia's formula (QTcF) >450 msec (or QTcF >480 msec in participants with bundle branch block).

- QTcF is the QT interval corrected for heart rate according to Fridericia's formula that is selected for this study. It is either machine-read or manually over-read when not automatically machine read. This specific formula must be used to determine eligibility and discontinuation for an individual participant.
- 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.

Note: Where a single ECG demonstrates a prolonged QTcF interval, obtain two more ECGs readings at a minimum of 2 minutes apart over a brief recording period (e.g., 5-10 minutes), The average of the triplicate QTcF measurements should be used to determine eligibility

8. **Unstable or life threatening cardiac disease:** Participants with any of the following would be excluded:
   - Myocardial infarction or unstable angina in the 6 months prior to Screening Visit 1
   - Unstable or life threatening cardiac arrhythmia requiring intervention in the 3 months prior to Screening Visit 1
   - New York Heart Association (NYHA) Class IV Heart failure
9. **Other diseases/abnormalities**: Participants with (historical or) current evidence of clinically significant, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant at risk through participation, or which could affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
10. **Eosinophilic disease:** Participants with other conditions that could lead to elevated eosinophils such as Hypereosinophilic syndromes including Eosinophilic Granulomatosis with Polyangiitis (EGPA, also known as Churg-Strauss Syndrome), or Eosinophilic Esophagitis.
11. **Parasitic infection:** Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening Visit 1.
12. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to Screening Visit 1 (Participants that had localized carcinoma of the skin or cervix which was resected for cure will not be excluded).

    Note: for South Korea: Korean participants with a diagnosis of malignancy within 5 years of Visit 1 are excluded.
13. **Immunodeficiency:** A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of corticosteroids taken for COPD.
14. **Liver disease:** Cirrhosis or current unstable liver disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal 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) is acceptable if the participant otherwise meets entry criteria.

Prior/Concomitant Therapy

15. **Previous mepolizumab studies:** Participants who have received interventional product in previous mepolizumab studies are excluded.
16. **Monoclonal antibodies:** Participants who have received any monoclonal antibody within 5 half-lives of Screening Visit 1
17. **Investigational medications:** Participants who have received an investigational drug within 30 days of Visit 1, or within 5 drug half-lives of the investigational drug,

whichever is longer (this also includes investigational formulations of a marketed product).

18. **Oral corticosteroids:** Participants who have received short term use of oral corticosteroids within 30 days of Visit 1

Other Exclusions

19. **Hypersensitivity:** Participants with a known allergy or sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates participation in the study or intolerance to another monoclonal antibody or biologic including history of anaphylaxis to another biologic
20. **Non-compliance**: Participants at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
21. **Questionable validity of consent**: Participants with, conditions that will limit the validity of informed consent to participate in the study, e.g uncontrolled psychiatric disease or intellectual deficiency.
22. **Drug or alcohol abuse**: A known or suspected history of alcohol or drug abuse within 2 years prior to Screening Visit 1.
23. **Affiliation with Investigator Site:** Is an Investigator, sub-Investigator, study coordinator, employee of a participating Investigator or study site, or immediate family member of the aforementioned that is involved in this study.
24. **COVID-19: a**- 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.

    b- 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.

5.3. Randomization Criteria

5.3.1. Randomization Inclusion Criteria

At Visit 2, those participants who continue to meet the inclusion/exclusion criteria and who meet the randomization inclusion/exclusion criteria will be randomized and commence the study intervention period until the target of approximately 800 randomized participants is reached.

1. **Blood eosinophil count:** Participants that do not have a historical blood eosinophil count that satisfies screening inclusion criterion 2 (Section 5.1) must have Screening Visit 1 blood eosinophil count ≥150 cells/µL.

2. **Electronic Diary Compliance:** Compliance with completion of the e-diary defined as completion of all questions on 5 or more days out of the 7 days immediately preceding Visit 2.

5.3.2. Randomization Exclusion Criteria

1. **COPD stability:** Participants who have pneumonia, exacerbation, lower respiratory infection during the Run-in period.
   Note: Participants may be re-screened 4 weeks after their exacerbation is resolved and only after written approval to proceed with re-screening from the study Medical Monitor.
2. **Laboratory abnormality:** Evidence of clinically significant abnormality in the hematological or biochemical screen at Visit 1, as judged by the Investigator.
3. **Liver function test (LFT):** Participants who meet the following based on results from sample taken at Screening Visit 1:

   Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)

   Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

   Cirrhosis or current unstable liver or biliary disease per Investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice.

   NOTES: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria

4. **Pregnancy:** Participants who are pregnant or breastfeeding. Participants should not be randomized if they plan to become pregnant during the time of study participation.

5. **COVID-19**: **a**- Participants that had an active COVID-19 infection during the Run-in period, either laboratory confirmed or according to the investigator's medical judgment.

   Note: Participants 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.

   b- 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.

6. **12-lead ECG:** Participants with a QT interval, from the ECG conducted at **Visit 2**, corrected with Fridericia's formula (QTcF) >450 msec (or QTcF >480 msec in participants with bundle branch block).

Note: Where a single ECG demonstrates a prolonged QTcF interval, obtain two more ECGs readings at a minimum of 2 minutes apart over a brief recording period (e.g., 5-10 minutes). The average of the triplicate QTcF measurements should be used to determine eligibility for randomization.

5.4. Screen and Run-in Failures

Screen failure: Screening Visit 0 and Screening Visit 1

Screen failures are defined as participants who consent to participate in the study, have at least one Screening Visit 0 assessment but who are not subsequently randomized.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Participants will be assigned a participant number at the time the informed consent is signed.

A participant, who is assigned a participant number at Screening Visit 0 but does not have any Screening Visit 1 procedures, will be considered a Screen failure at Screening Visit 0.

The study interactive web response system (IWRS) will be contacted to report screen failures at Screening Visit 0. The following information will be collected for participants who are screen failures at Screening Visit 0:

- Date of ICF signature
- Demographic information including race, year of birth, gender and child bearing potential
- Participant number
- Reason for screen failure
- Inclusion/Exclusion criteria
- Hematology sample collection
- Historical eosinophil collection
- Investigator signature page
- SAEs considered as related to study participation or related to any GSK product. **China only:** All SAEs will be collected.

Participants who continue to Screening Visit 1 and have at least one assessment but who are not subsequently randomized will be considered screen failures at Screening Visit 1.

In addition to information collected for screen failures at Screening Visit 0 (above) the following information will be collected for screen failures at Screening Visit 1:

- Date of Screening Visit 1
- Reason for screen failure
- SAEs considered as related to study participation or related to any GSK product. **China only:** All SAEs will be collected.

The IWRS will be contacted to report screen failures at Screening Visit 1.

Run-in failure

Any participant who completes Screening Visit 1 enters the Run-in period and completes at least one Visit 2 procedure but is not randomized is classified as a Run-in failure

The IWRS will be contacted to report Run-in failures. In addition to the information above, the following information will be collected for Run-in failures:

- Date of Visit 2
- Reason for Run-in failure (e.g., COPD exacerbation, lower respiratory tract infection [LRTI], pneumonia)

Additional information related to data collection for, screen failures at Screening Visit 0 or Screening Visit 1, and Run-in failures can be found in the eCRF completion guidelines.

Re-screening of screen failure and run-in failure participants will be permitted; however, advance written approval to proceed with re-screening a participant must be obtained from the Medical Monitor.

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

CCI [redacted] Further details of dose preparation and administration can be found in the current version of the IB and the SRM.

Table 1 Study Interventional products

ARM Name	Mepolizumab 100 mg	Placebo
Intervention Name	Mepolizumab 100 mg SC	Placebo
Type	Biologic	N/A
Dose Formulation	CCI [redacted]	
Unit Dose Strength(s)	100 mg/mL; 1.0 mL (deliverable)	1.0 mL deliverable
Dosage Level(s)	100 mg once every 4 weeks	Placebo once every 4 weeks
Route of Administration	SC injection	SC injection
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Study Intervention will be provided in pre-filled safety syringe. Each pre-filled safety syringe will be labelled as required per country requirement.	Study Intervention will be provided in pre-filled safety syringe. Each pre-filled safety syringe will be labelled as required per country requirement.

6.1.1. Medical Devices

- Instructions for use of the pre-filled safety syringe are provided in the SRM
- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the Investigator throughout the study (see Section 8.3.7)
- The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are injection devices:
  - A prefilled syringe contained within a safety syringe. The devices used in the study are representative of the devices marketed for the product.
  - CCI [redacted].

- CCI [redacted].

The Instruction for use (IFU) of these injection devices are provided in the SRM. The instructions were developed and optimised as a result of formative human factors studies and are representative of those that are planned for the product.

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention. Further details are provided in the SRM.
2. Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the SRM
5. 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.
6. Precaution will be taken to avoid direct contact with the study intervention. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally randomized using an IWRS before the study is initiated. Log in details and directions for accessing the IWRS will be provided to participating sites.

At Visit 2 (Day 1) those participants who meet the randomization eligibility criteria will be randomized in a 1:1 ratio to receive one of the following interventions every 4 weeks:

- Mepolizumab 100 mg SC

- Placebo SC

A unique Participant Number will be assigned to participants who have consented. This unique participant number will be used to identify the individual participant throughout the study and will not be re-assigned to any other participant.

Participants will be assigned to study intervention in accordance with the randomization schedule. Once a Randomization number has been assigned to a participant, it cannot be reassigned to any other participant in the study.

The Randomization schedule will be generated using a validated Randomization software. Separate Randomization schedules will be created for each country. Equal numbers of participants will be allocated to each intervention arm.

Details of how to use the IWRS to register and randomize participants will be provided in the SRM.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded GSK must be notified within 24 hrs after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

A participant must discontinue IP but may continue in the study if the participant's intervention assignment is unblinded by the investigator or treating physician. The event or condition which led to the unblinding will be recorded in the eCRF.

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

6.4. Study Intervention Compliance

Study intervention will be administered at the study site by a designated member of the site staff. Drug dispensing/accountability logs will be maintained by a designated member of the site staff.

- Participants are dosed under medical supervision at the site, they will receive mepolizumab 100 mg SC or matching placebo, provided in a pre-filled safety syringe, directly from the Investigator or designee. The date and time of each dose administered in the clinic will be recorded in the participant's source documents. The study interventional product and study participant identification will be

confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

- For the first three administrations participants will be monitored for 1 hour after receiving study interventional product. For subsequent administrations of interventional product, participants will be monitored according to the monitoring policies for the center or vendor for home visits.
- 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 or at the participant's home (if a home visit) 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.
- Administration of study intervention will be documented in the source documents and reported in the CRF.
- **NOTE:** Where applicable refer to Appendix 10 and the SRM for details on COVID-19 pandemic measures and home healthcare for study assessments and study intervention.

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 pre-screening/screening 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.

It is permissible for participants to be vaccinated against COVID-19 with vaccines authorized or approved by the local regulatory authority; vaccination with an unapproved or unauthorized COVID-19 vaccine (i.e., a candidate vaccine) is not permissible.

6.5.1. Rescue Medicine

Participants will be supplied with the short-acting bronchodilator salbutamol Metered Dose Inhaler (MDI) or nebules as rescue medication.

Although the use of rescue short-acting bronchodilators is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least 4 hours prior to spirometry testing (see Schedule of Activities, Section 1.3 and Section 8.1.4).

6.5.2. Permitted Medications and Non-Drug Therapies

The **COPD medications** listed below are permitted during the treatment period while the participant is on IP. The requirements for study inclusion with regards to this medication list are described in detail by Study Inclusion Criterion 5:

- If taken as standard of care therapy prior to Visit 1 the following are permitted:
  - inhaled corticosteroids
  - inhaled long-acting muscarinic antagonists
  - inhaled long-acting beta$_2$-agonists
  - methylxanthines
  - phosphodiesterase-4 (PDE-4) inhibitor
  - oral corticosteroids (chronic use only)
  - leukotriene receptor antagonists (Singulair)
- Oral or injectable corticosteroids (short course ≤14 days) only for the short term treatment of COPD exacerbations and/or pneumonia
- Antibiotics (short course ≤14 days) for the short term treatment of COPD exacerbations and/or pneumonia
- Mucolytics such as acetylcysteine
- Long term oxygen therapy (LTOT). To be eligible to enter the study participants who are on LTOT must be using at a flow rate of ≤2 L/minute at rest over 24 hours. However, oxygen therapy may be adjusted as deemed medically necessary at any time during the study. Oxygen therapy must be captured on the concomitant medication page of the eCRF. Supplemental oxygen is recommended for patients who exhibit oxyhemoglobin desaturation with rest or exertion (*e.g.* SaO2 ≤88%) while breathing room air.
- Maintenance phase of pulmonary rehabilitation treatment (participants **are not** allowed to initiate treatment during the study).
- Rescue medication for prn use e.g. salbutamol or ipratropium.

The following **non-COPD medications** are permitted during the study (for example):

- Medications for rhinitis (e.g. intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)

- Topical and ophthalmic corticosteroids
- Unplanned localized corticosteroid injections (e.g. intra-articular and epidural)
- Vaccinations (Influenza vaccine, Pneumonia vaccine, Shingles vaccine, etc). Administration of influenza and pneumonia vaccines should be considered based on clinical discretion of the Investigator and local/national guidelines. Vaccines will be captured on the concomitant medication pages of the eCRF
- Allergy immunotherapy
- Antibiotics for short-term treatment (≤14 days) of acute infections. Long term treatment with antibiotics is not allowed
- Systemic and ophthalmic beta-blockers
- Smoking cessation treatments
- Cough suppressants
- Anti-depressants and anxiolytics
- Continuous Positive Airway Pressure (CPAP) and Bi-Level Positive Airway Pressure (BiPAP)
- **Note:** Immune-suppressants for conditions other than COPD are allowed if they have been stable for the 3 months prior Screening Visit 1 and after discussion with the study Medical Monitor.

6.5.3. Prohibited Medications and Non-Drug Therapies

Medications noted as part of exclusion criteria are prohibited for the duration of the treatment period.

Eligible participants are expected to continue their Baseline maintenance COPD medications during the run-in period and throughout the intervention period. Where spirometry is performed (See SoAs in Section 1.3.1and Section 1.3.2), participants will refrain from taking their morning dose of their maintenance COPD medications until instructed to do so by clinic personnel.

Rescue medication (i.e. salbutamol or ipratropium) must also be withheld for at least 4 hours before visits when spirometry is performed (see SoA Section 1.3), and prior to reversibility testing at Visit 1.

COPD medications and non-drug therapies that are prohibited during the randomized phase of the study:

- Acute phase of pulmonary rehabilitation (at any time during the study including Run-in)
- Long term systemic antibiotic therapy (antibiotics used for ≤14 days for acute infections or for exacerbations or pneumonia are allowed).
- Monoclonal antibodies
- Chronic oral corticosteroids for non-COPD treatment

  Note: Chronic macrolide therapy is permitted. Participants taking chronic macrolides at Visit 1 should continue the macrolide throughout the duration of the study.
- Experimental anti-inflammatory drugs (non-biologicals) or other investigational products (biologic or non-biologic) within either 30 days or five drug half-lives prior to Visit 1, whichever is longer.
- Other investigational products (participants must have not received investigational products for 1 months or 5 half-lives prior to Visit 1, whichever is longer)
- Radiation therapy is excluded for 12 months prior to Visit 1 and throughout the study

6.6. 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 participant's medical condition. No additional doses of mepolizumab treatment will be provided by GSK at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If a participant permanently discontinues interventional product before the end of the protocol specified randomized intervention period, every effort will be made by the Investigator to encourage the participant to remain in the study and to complete all remaining study visits. Participants will be provided with the option to continue to have regularly scheduled in-clinic visits or to have regularly scheduled phone visits. The Investigator must document the reason for discontinuation of IP in the eCRF. The principal Investigator/ site staff should continue contact with the participant at the protocol designated visit time intervals to complete study assessments. The required study assessments will depend on whether the participant is attending an in-clinic visit or a scheduled phone visit. At a minimum, an assessment of exacerbations, AEs, SAEs, and concomitant medications will be completed. Further details are provided in the SRM.

The Investigator should make every effort to have the participant return to the clinic 4 weeks after the participant permanently discontinues IP in order to complete the Discontinuation from IP Visit.

The primary reason for discontinuation from IP will be recorded in the eCRF.

Participants should permanently discontinue IP, but not the study, if the following criteria are met:

- Meets any of the protocol-defined liver chemistry stopping criteria, identified during the study or identified during routine standard of care assessments outside of the study (See Section 7.1.1 and Appendix 7)
- ECG: Clinically significant abnormality identified during the study that meet the QTc stopping criteria described in Section 7.1.2
- Pregnancy: Positive pregnancy test (See Appendix 5)

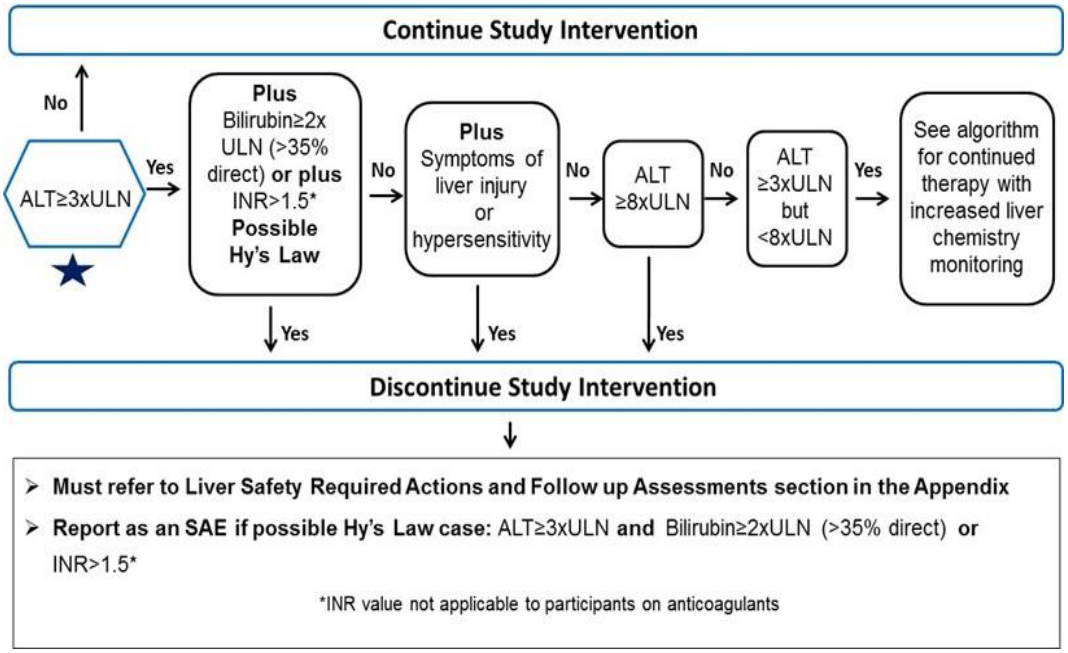
7.1.1. Liver Chemistry Stopping Criteria

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

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

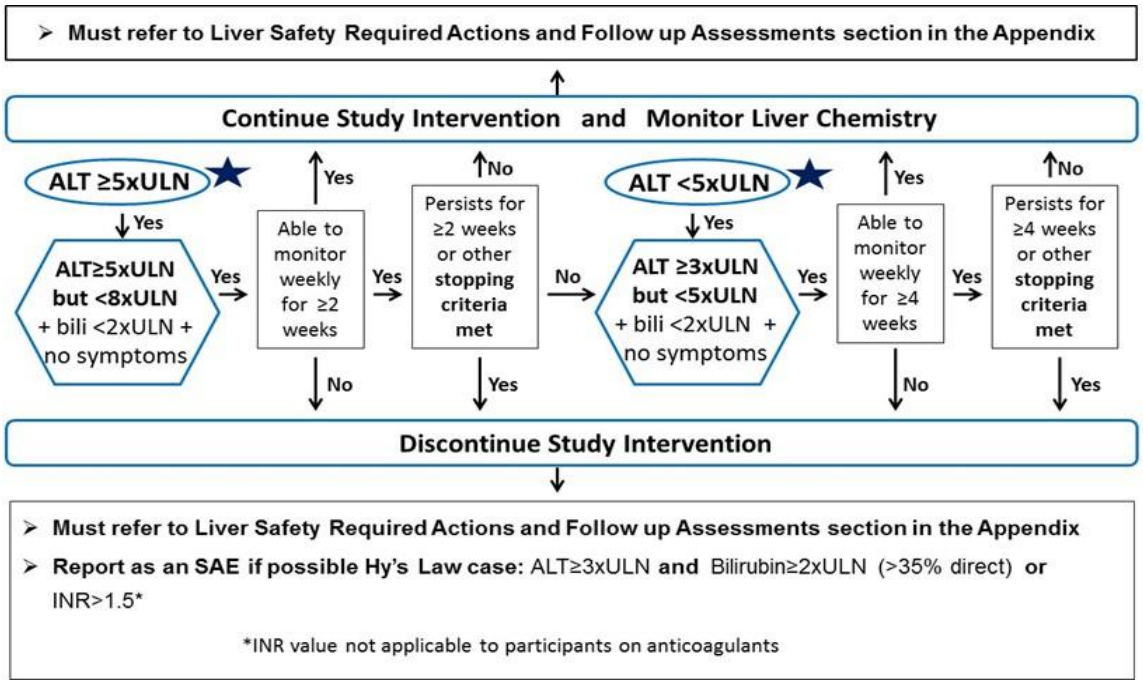
- a participant meets one of the conditions outlined in the algorithm below
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

Liver Chemistry Stopping Algorithm



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

Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for participants with ALT ≥3xULN but <8xULN and who do not meet any liver stopping criteria



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

Refer to Appendix 7: Liver Safety Required Actions and Follow up Assessments for required actions, monitoring and follow up assessments for any event that met liver stopping or liver monitoring criteria.

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

Study treatment 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

- The QT correction Fridericia formula must be used for each individual participant to determine eligibility for and discontinuation from IP. This formula may not be changed or substituted once the participant has been enrolled.

A participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study treatment intervention but not from the study:

- QTcF >500 msec OR Uncorrected QT >600 msec
- Change from baseline of QTcF >60 msec

For patients with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTcF with Bundle Branch Block	**Discontinuation QTcF with Bundle Branch Block**
<450 msec	>500 msec
450 – 480 msec	≥530 msec

7.1.3. Temporary Discontinuation

If a participant becomes infected (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.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may prematurely discontinue study intervention product and withdraw from the study at any time at his/her own request, or at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Participants may withdraw from the PK sub-study and remain in the study.

Participants who permanently discontinue IP are not required to withdraw from the study. If a participant must permanently discontinue IP, every effort should be made by the Investigator/site staff to keep the participant in the study to collect important efficacy and safety data. Participants who have permanently discontinued IP and have not withdrawn consent may continue in the study to complete all remaining protocol specified visits by continued in-clinic visits (or home healthcare, if applicable) or by phone contact.

For participants who discontinue IP but remain in the study, an IP discontinuation Visit should be conducted as shown in SoA. See SoA (Section 1.3) for data to be collected at the time of IP discontinuation. If for any reason those participants later withdraw from the study, a withdrawal from the study Visit should be conducted as shown in the SoA. Additional details will be given in the SRM.

For participants who discontinue IP and withdraw from the study at the same time, the Withdrawal from study Visit should be conducted as per SoA.

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.

Any participant who withdraws from the study prior to their planned Completion of Study date (defined in Section 4.4) will be considered to have missing data from the date of study withdrawal up to their planned Completion of Study date.

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 staff.

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.

7.4. Reasons for IP Discontinuation and/or Study Withdrawal

The primary reason for IP discontinuation and/or study withdrawal will be recorded in the eCRF. When a participant withdraws consent, the Investigator must document the reason (if specified by the participant) in the eCRF.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoAs (Section 1.3).

NOTE: Where applicable refer to Appendix 10 and the SRM for details on COVID-19 pandemic measures and home healthcare for study assessments.

- 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 Visit 0 and Screening Visit 1 evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a Screening log and complete details in the eCRF data base to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
    - The order of assessments at clinic visits is listed in the SRM

Screening and Critical Baseline Assessments

Screening Visit 0

During Screening Visit 0, site staff must provide informed consent to the study participant. Informed consent for an optional genetic sample, where permitted, is also provided at this visit.
China and US only: Informed consent for the optional PK sub-study in China and the US can also be provided at this visit.

A mandatory hematology blood sample is collected at this visit and will be used to assess Inclusion Criterion 2 (a blood eosinophil count of ≥300 cells/μL at Screening Visit 0).

A participant number will be assigned at the time the informed consent form (ICF) is signed. No study related procedures may be performed until the ICF document has been signed by the participant.

During Screening Visit 0, the following assessments are performed:

- Demography including year of birth, gender, race, child bearing potential and ethnicity
- COPD and all concomitant medications review
- Hematology blood sample (for eosinophil count) is collected.
- Review of inclusion/exclusion criteria
- Historical blood eosinophils: Where several historical blood eosinophil counts are obtainable, the highest eosinophil count should be recorded in the eCRF for each of the following specified periods: ≥1 to <6 months and 6 to12 months. In order to meet the Inclusion Criteria #2 (Section 5.1), a historical blood eosinophil measurement must meet the following: It must have been measured between 12 months and 1 month prior to Visit 0 and it must not have been measured within 14 days of a COPD exacerbation. If, in either of the 2 specified periods, the only historical documented blood eosinophil count is associated with a COPD exacerbation, then this eosinophil count cannot be used for inclusion in the study but should be recorded in the eCRF. Refer to the SRM for more information.

For Screening Visit 0, SAEs considered as related to study participation (including concomitant medications related to the SAEs) must be reported. For **China** all SAEs will be reported after signing of ICF.

All clinic visits from Screening Visit 0 to Exit Visit must be registered in the IWRS and the relevant eCRF form completed.

Critical procedures performed at Screening Visit 1

Results from the hematology testing at Screening Visit 0 must be obtained before performing Screening Visit 1. Participants who do not meet the inclusion criteria of ≥300 eosinophil/µL cannot proceed to Screening Visit 1 and will be considered screen failures. The following critical assessments will be conducted at Screening Visit 1:

- Medical history including COPD (including date of diagnosis and COPD type (emphysema or chronic bronchitis), COPD exacerbation history, smoking status, smoking cessation counselling, previous and/or current medical conditions. Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening as well as family history of premature cardiovascular disease.
- A hematology blood sample must be drawn from participants who do not have documentation of a historical blood eosinophil count ≥150 cells/µL in the 12 months prior to Screening Visit 0.
- Screening Visit 1 spirometry including pre- and post-albuterol/salbutamol responsiveness testing, (see Section 8.1.4.2)
- Parasitic screening, total IgE as described in the SoA
- Concomitant medication review; COPD maintenance medications from the year prior to Screening Visit 1 and all other medications within the 3 months prior to Screening Visit 1.
- Complete physical examination including height and weight
- 12-Lead ECG
- Modified Medical Research Council Grading System (mMRC): The participant's degree of dyspnea to different levels of activity will be rated on the five point mMRC scale. The mMRC, administered by an interviewer, asks participants to rate how breathless they are on a 5-point Guttman scale.
- Vital signs and pulse oximetry at this visit only
- Urine pregnancy test if applicable
- Clinical chemistry
- Register and train participant on the use of eDiary. Instruct participant to complete the daily evening eDiary from Screening Visit 1 and throughout the study
- Review inclusion/exclusion criteria assessments
- Review exacerbations, SAEs if related to study participation. (for **China** all SAEs will be reviewed)
- Provide medical problems and healthcare utilization worksheet
- Dispense rescue medication
- Record Visit in the IWRS

Critical procedures performed at Visit 2 (Randomization, first study intervention Visit)

The following critical assessments will be conducted at Visit 2:

- Review AEs and SAEs
- Review exacerbations during the Run-in period
- COPD and Concomitant medication review
- Review and assess compliance with completing the eDiary during the Run-in period
- Vital signs and 12-Lead ECG
- Review randomization inclusion and exclusion criteria (Section 5.3)
- Urine pregnancy test, if applicable
- Hematology, clinical chemistry, immunogenicity and blood biomarker
- CAT, SGRQ-C, EQ-5D-3L, and patient global rating of COPD severity questionnaires in eDiary
- Spirometry
- Review COPD symptoms summary report through the vendor's web-based portal
- Provide and review medical problems and healthcare utilization worksheet
- Dispense rescue medication
- Optional genetics sample can be collected at Visit 2 or any visit after.
- **China and US only:** Optional PK sample is collected at this visit. See SoA Section 1.3 for collection of other PK samples during the study.
- Register and randomize participant in the IWRS
- Administer study Interventional product as per SoA

8.1. Efficacy Assessments

8.1.1. Moderate and Severe COPD Exacerbations

Moderate exacerbations are defined per protocol as clinically significant exacerbations that require treatment with oral/systemic corticosteroids and/or antibiotics.

Severe exacerbations are defined per protocol as clinically significant exacerbations that require in-patient hospitalization (i.e., ≥24 hrs) or result in death.

The decision to treat moderate exacerbations should be corroborated by review of data from the daily symptoms eDiary to confirm that the exacerbation was associated with deterioration of symptoms.

For safety reasons alerts will be programmed into the eDiary to encourage the participant to contact the investigator if their COPD symptoms worsen. The site will also receive notification of the alert. An alert itself will not be classified as a moderate exacerbation unless it resulted in subsequent treatment for the worsening of symptoms meeting the definition above.

8.1.1.1. Guidelines for Identifying Symptom Defined COPD Exacerbations

The following are symptoms used to ascertain an exacerbation of COPD:

Worsening of two or more of the following major symptoms for at least two consecutive days:

Dyspnea

Sputum volume

Sputum purulence (color)

OR

Worsening of any one major symptom together with any one of the following minor symptoms for at least two consecutive days:

Sore throat

Colds (nasal discharge and/or nasal congestion)

Fever (oral temperature >37.5°C) without other cause

Increased cough

Increased wheeze

Site staff will have access to a symptom summary report through a web-based portal. The symptoms summary report will indicate when symptoms meet the above criteria.

If a participant is determined to have an exacerbation it should be treated per protocol as described in Section 8.1.2

8.1.2. Exacerbation Treatment

If in the opinion of the Investigator/treating physician, the exacerbation is severe enough to warrant the need for oral corticosteroids (with or without antibiotics) the following guidelines should be used.

- The duration of treatment with oral corticosteroids should be ≤14 days (dose and type according to local practice)
- The duration of treatment with oral corticosteroids should not exceed 14 days unless given approval by the Medical Monitor
- Any course of oral corticosteroids started within 7 days of finishing a previous course will be considered as treatment for a single exacerbation

If, in the opinion of the Investigator/treating physician, there is evidence of respiratory bacterial infection that warrants treatment with antibiotics the following guidelines should be followed:

- The duration of treatment with antibiotics should be 7 to 14 days (dose and type according to local practice). If first line antibiotic treatment fails and additional

antibiotics are used, the total duration of antibiotic treatment should not exceed 30 days unless given approval by the Medical Monitor.

- Any course of antibiotics started within 7 days of finishing a previous course will be considered as treatment for the original exacerbation (i.e. a single exacerbation).

Note: *Use of antibiotics for the treatment of upper or lower respiratory tract infection is not considered a COPD exacerbation unless worsening of COPD symptoms are documented by the Investigator in the participant's medical notes.*

All medications used for the treatment of exacerbations must be recorded in the source documents and the exacerbation page of the eCRF.

Exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of an SAE.

8.1.3. Health Related Quality of Life Assessments

All Clinical Outcomes Assessment (COA) efficacy endpoint assessments completed at study visits will be completed using the eDiary. Participants will complete the following PROs at study visits where indicated in the Schedule of Assessments (Section 1.3). Clinician rated response to therapy will also be collected on the eDiary.

- The COPD Assessment Test
- The St. George's Respiratory Questionnaire for COPD Patients
- Patient Global rating of COPD severity and Global Rating of change in COPD
- Patient and Clinician rated response to therapy

8.1.3.1. COPD Assessment Test (CAT)

The CAT [Jones, 2009; Jones, 2012] is a short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, participants rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact.

The CAT should be completed in the clinic at each scheduled in clinic visit, before any other visit procedures, as indicated in the SoA (Section 1.3)

8.1.3.2. St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)

The SGRQ-C is a 40-item patient questionnaire, designed to measure health impairment by addressing the frequency of respiratory symptoms (questions 1-7) and the patient's current state (questions 8-14). Higher scores indicate greater impairment of health. The SGRQ-C is derived from the original SGRQ, and produces scores equivalent to the SGRQ instrument [Meguro, 2007]. The SGRQ-C is designed for supervised self-administration which means that the participant should answer the questionnaire by themselves, but that site staff can provide support if required. It is appropriate to help

clarify a question but do not provide an answer. If participants have difficulty reading questions may be read out loud. The participant's response should not be challenged.

Participants must complete the questionnaire while in the clinic for their scheduled study visit. The SGRQ-C should be administered after CAT and before any other study procedures at Randomization (Visit 2) and at additional visits indicated in the Schedule of Assessment (Section 1.3).

8.1.3.3. Daily Symptom Diary

Using the eDiary, participants will complete a daily symptom diary (each evening) consisting of:

- items from EXACT;
- additional symptoms questions (related to symptoms of an exacerbation);
- rescue medication use; and
- night time awakenings

Participants will be trained to use the eDiary at Visit 1 and will complete the eDiary throughout the study.

EXAcerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcomes (EXACT) and Evaluating Respiratory Symptoms in COPD (E-RS: COPD)

The Exacerbation of Chronic Pulmonary Disease Tool-Patient Reported Outcomes (EXACT) is a 14-item participant reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of symptoms suggestive of an exacerbation of disease in patients with COPD. EXACT captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the participant [Leidy, 2011].

The EXACT questions will be the first questions presented for completion each evening at bedtime in the eDiary.

The daily recording of information allows an assessment of the underlying day to day variability of a participant's symptoms and facilitates the detection of symptom worsening that may be indicative of a COPD exacerbation. The total score for EXACT ranges from 0-100, higher scores indicate more severe symptoms. The entire instrument is intended to be completed in about 3 minutes or less (typically the time required for completion decreases as the participant becomes more familiar with the tool and the eDiary).

The Evaluating Respiratory Symptoms in COPD (E-RS: COPD) consists of 11 items from the 14 item EXACT instrument. E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough, sputum production, chest congestion, and chest tightness. The E-RS: COPD has a scoring range of 0-40, higher scores indicate more severe symptoms [Leidy, 2014].

Three subscales of the E-RS: COPD are used to describe different symptoms; breathlessness, cough and sputum, and chest symptoms [E-RS™: COPD, 2016].

Additional symptoms questions

In addition to the collection of EXACT, participants will also complete 5 additional daily diary questions to provide the information on other symptoms suggestive of an exacerbation: sputum purulence (color), wheezing, sore throat, colds (nasal discharge and/or nasal congestion) and fever without other cause.

These additional symptoms questions, combined with EXACT responses to questions on dyspnea, cough and sputum quantity will be used to trigger prompts to both site staff and patients about symptom changes, as described in Section 8.1.1.1, that may be indicative of an exacerbation.

Rescue medication use

The number of occasions of rescue medication use will also be captured in the daily eDiary.

Night time awakenings

Data regarding nighttime awakenings will also be captured in the daily eDiary.

8.1.3.4. Patient Global Rating of COPD Severity and Patient Global Rating of Change in COPD

Participants will complete the Global Rating of COPD Severity as per SoA (Section 1.3). This single global question will ask participants to rate their severity of COPD on a four point scale (mild, moderate, severe, very severe).

Participants will complete a Global Rating of Change in COPD (overall disease) question at specified scheduled visits as per SoA, subsequent to randomization including the Exit Visit (or IP Discontinuation Visit). Response options are on a 7 point Likert scale ranging from much better to much worse.

8.1.3.5. Patient and Clinician Rated Response to Therapy

The clinician will be asked to rate the response to therapy at the visits specified in SoA (Section 1.3). This is an overall evaluation of response to intervention, conducted separately by the Investigator using a rating scale. A seven-point scale score is used with the following definitions: 1 = significantly improved; 2 = moderately improved; 3 = mildly improved; 4 = no change; 5 = mildly worse; 6 = moderately worse; and 7 = significantly worse.

8.1.4. Spirometry and Bronchodilator Responsiveness Testing

8.1.4.1. Spirometry

Spirometry measurements will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the ATS [Miller, 2005]. All sites will use their own spirometry equipment. All participants will have pre and post-bronchodilator spirometry performed at Screening Visit 1 and pre-bronchodilator spirometry at all other scheduled clinic visits during the treatment period as indicated in

the SoA (Section 1.3). For FEV_1 and FVC determinations, at least 3 acceptable spirometry efforts (with no more than 8) should be obtained. Acceptable spirometry efforts should have a satisfactory start of test and end of test (i.e. a plateau in the volume-time curve) and be free from artefacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Additional details about acceptable quality for spirometry testing are provided in the SRM.

Spirometry must be performed as follows:

Started between 6:00AM and 11:00 AM

- After completing questionnaires at visits where these assessments are captured (as specified in the SoA)
- After withholding salbutamol for ≥4 hrs
- After withholding ipratropium for ≥4 hrs
- After withholding the morning dose of maintenance COPD medications
- Prior to IP dosing

Participants should refrain from smoking for 1 hour prior to each pulmonary function test.

Participants should abstain from drinking beverages with high levels of caffeine such as tea and coffee for 2 hrs prior to each pulmonary function test.

A full description of the timing and conduct of spirometry procedures is provided in the SRM.

8.1.4.2. Bronchodilator Responsiveness Testing

At the Screening Visit 1, both pre- and post-salbutamol spirometry will be obtained to determine participant eligibility.

Bronchodilator responsiveness testing will be completed as follows:

- Following pre-salbutamol spirometry (a minimum of three acceptable spirometry efforts), the participant will self-administer 4 puffs of salbutamol MDI. Three acceptable spirometry efforts will be obtained approximately 10 to 30 minutes after salbutamol administration.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. In consideration of the safety profile of mepolizumab in the IB, for participants continuing in the study beyond 52 weeks (as per the SoA in Section 1.3.2), vital signs and clinical safety

laboratory assessments are taken at less frequent intervals in the second year (Week 52 to 104; Section 1.3.2) than in the first year (Week 0 to 52; Section 1.3.1).

8.2.1. Physical Examinations

Complete physical examinations will be performed at scheduled visits as noted in the SoA (Section 1.3).

- 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 at Screening Visit 1. For subsequent visits, only weight will be measured.
- Investigators should pay special attention to historical clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Oral or skin temperature, pulse rate and BP will be assessed.
- Blood pressure and pulse measurements will be assessed in the resting state with a completely automated device. (Manual techniques will be used only if an automated device is not available).
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and should be taken before blood collection for laboratory tests.

8.2.3. Electrocardiograms

- A single 12-lead ECG and rhythm strip will be obtained at scheduled visits as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals (if a machine read QTcF is unavailable, QTcF will be manually calculated). All sites will use their own ECG equipment. All results will be recorded after measurement of vital signs and prior to spirometry.
- If a routine single ECG demonstrates a prolonged QT interval, obtain two more ECG readings over a brief recording period (e.g., 5-10 minutes), with each recording separated by at least 2 minutes. The averaged QTcF values of the three ECG readings should be used to determine whether the patient should be discontinued from intervention product (but not from the study). Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary. These ECGs in question should be scanned and sent to the Medical Monitor.
- All ECG measurements will be made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading.
- The Investigator, a designated sub-Investigator, or other appropriately trained site personnel will be responsible for performing each 12-lead ECG. The Investigator

must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

- If a clinically relevant arrhythmia, infarct pattern or conduction defect is documented at Screening, the PI will need to record in eCRF prior knowledge of the ECG pattern.

8.2.4. Medical Problems and Concomitant Medications

Participants will be instructed to record any medical problems and the medications used to treat them over each day in the medical problems and health care utilization worksheet. These entries will be reviewed by the site staff at each study visit and recorded in the eCRF as AEs and concomitant medications as appropriate.

8.2.5. Pneumonia

All pneumonias should be confirmed by the presence of new infiltrate on chest X-ray and captured on the AE/SAE page of the eCRF.

Investigators and site staff should remain vigilant for the possible development and diagnosis of pneumonia as the clinical features of such infections overlap with the symptoms of COPD exacerbations. For all suspected cases of pneumonia, Investigators should confirm the diagnosis by obtaining a chest X-ray or documentation of the result of a chest X-ray performed outside of the clinic site. Appropriate therapy should be initiated for confirmed pneumonia. Confirmation by chest X-ray should occur within 48 hours of suspected pneumonia.

8.2.6. Clinical Safety Laboratory Assessments

Refer to Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. Tests must be performed by the designated central laboratory.

- 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 eCRF. 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 28 days after the last dose of treatment 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 etiology should be identified and the Medical Monitor notified.
- All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the laboratory manual and the SoA.

- If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinically significant by the Investigator (e.g., SAE or AE) the results must be recorded in the participant's eCRF. Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

A blood sample for hematology will be collected at scheduled study visits, including premature discontinuation of IP. After Randomization, neither the site staff nor GSK personnel will be sent results from the central laboratory for: absolute and differential values for eosinophils, lymphocytes, basophils, neutrophils and monocytes. However, sites will be sent total white blood counts throughout the study. This must also be applied to hematology results received from a local laboratory.

Routine non-fasting clinical chemistry including serum glucose and serum potassium levels will be performed as per SoA. In the event of premature discontinuation from IP or from the study a sample should be collected at the IP Discontinuation/study Withdrawal Visit as specified in the SoA (Section 1.3).

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

COPD exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of an SAE.

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 7.1).

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

- Systemic reactions
- Local injection site reactions

In addition, the information as to whether an event met the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] and in Appendix 2 will be collected on the AE and SAE eCRF pages.

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

- **China only:** In China, all SAEs will be recorded from the time the consent form is signed until the Exit Visit/Study Withdrawal Visit at the time points specified in the SoA (Section 1.3).

- All SAEs will be collected from the start of study intervention until the Exit Visit/Study Withdrawal Visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to any GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of study intervention until the Exit Visit/Study withdrawal visit at the time points specified in the SoA (Section 1.3). Medical occurrences that begin before the start of intervention product but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hrs, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek 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 intervention product 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 4
- Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. 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 and non-serious AEs of special interest as defined in (Section 8.3), 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 4.

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 16 weeks 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 5.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3.6. Cardiovascular and Death Events

For any CV events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

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

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

8.3.7. Medical Device Deficiencies

Medical devices are being provided for use in this study. To fulfil regulatory reporting obligations worldwide, the Investigator or designee is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Appendix 8.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 4 of the protocol.

8.3.7.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiencies at any time after a participant has been discharged from the study, and such device deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Deficiencies is provided in Appendix 8.

8.3.7.2. Follow-up of Medical Device Deficiencies

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

8.3.7.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

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

8.3.7.4. Regulatory Reporting Requirements for Medical Device Deficiencies

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

8.3.8. Adjudication Committee

Independent external adjudication committees for all SAE reports and all potential MACE adverse events (CV death, non-fatal myocardial infarction [MI], non-fatal stroke)

will be utilized in this study to ensure external objective medical review of these events in a blinded fashion. The committee members will remain blinded to study intervention assignment. The adjudication plans are described in the charter, which is available upon request.

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. However, the Investigator should use clinical judgement in treating the symptoms of a suspected overdose, inform the Medical Monitor and record the overdose in the eCRF.

8.5. Pharmacokinetics

8.5.1. Optional pharmacokinetic sub-study in China and the US only:

Pharmacokinetic blood samples for the determination of mepolizumab plasma concentration will be collected at the timepoints indicated in the SoA (Section 1.3), from participants who sign the optional PK informed consent. Samples should be obtained prior to dosing on dosing days. The actual date and exact time of each blood sample collection will be documented in the eCRF and on the sample requisition form provided by the Central Laboratory. Additionally, the date and time of IP injection will be recorded in the eCRF.

8.5.2. Sample preparation and shipment

Details of PK sample preparation and shipment are described in the SRM.

8.5.3. Sample Analysis and Assay Method

Plasma analysis will be performed under the control of GSK- In Vitro / In Vivo Translation (IVIVT), the details of which will be included in the SRM. Concentrations of mepolizumab will be determined in plasma samples using the approved bioanalytical methodology. Raw data will be archived at the bioanalytical site. Quality control samples will be assayed with each batch of samples in order to assess the day-to-day performance of the assay.

8.6. Pharmacodynamics

Blood eosinophil counts will be recorded as part of the standard hematological assessments performed at the visits specified in the SoA (Section 1.3)

8.7. Genetics

China only: Genetic blood samples will **not** be collected from participants in China.

A 6 mL whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected, where permitted, from participants who have consented to participate in the genetics

analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

8.8. Biomarkers

China only: Blood biomarkers samples will **not** be collected from participants in China.

- Collection of samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from participants, where permitted, in this study as specified in the SoA:
  - Blood
- In addition, with the participant's consent and where permitted, samples will be stored and analysis may be performed on biomarkers thought to play a role in mepolizumab response, with COPD or related diseases, or to evaluate their association with observed clinical responses to mepolizumab.
- Additional whole blood and serum samples will be collected and may be used for future analyses.
- Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last Visit for the study at a facility selected by the sponsor to enable further analysis of biomarker responses to mepolizumab.

8.9. Immunogenicity Assessments

Antibodies to mepolizumab will be evaluated in blood samples collected from all participants according to the SoA. Additionally, blood samples should also be collected at the final treatment Visit from participants who discontinued intervention product or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Samples will be screened for antibodies binding to mepolizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to mepolizumab and/or further characterize the immunogenicity of mepolizumab.

The detection and characterization of antibodies to mepolizumab will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to mepolizumab will also be evaluated for mepolizumab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of mepolizumab.

Further details regarding sample collection and processing may be found in the SRM and lab manual.

8.10. Health Outcomes Assessments

8.10.1. Medical Resource Utilization and Health Economics

Health Care resource utilization, associated with unscheduled medical encounters, will be recorded by participants in a worksheet and collected in the eCRF by the Investigator and study-site staff for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected about unscheduled use of health care resources may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [e.g., intensive care unit, high dependency and usual care])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).
- Home visits (day and night time)
- Long term oxygen therapy

The resource utilization worksheet used by the participant to record all COPD-related health care contacts experienced since the last visit will be collected and reviewed by the Investigator or designee at the visits indicated in Section 1.3. The Investigator or designated staff should ask the participant if any of the health care contacts that are recorded on the worksheet were due to a COPD exacerbation. The Investigator can refer to his/her records to verify or supplement information given by the participant, if necessary. If any unscheduled healthcare contact is due to a COPD exacerbation, then the Investigator should ensure completion of the COPD Exacerbation section of the eCRF. Details regarding completion of the Healthcare Utilization worksheet are located in the SRM.

8.10.2. EuroQol questionnaire (EQ-5D-3L)

The EQ-5D-3L questionnaire will be completed via eDiary by participants at randomization and at scheduled visits as indicated in the SoA (Section 1.3).

The EQ-5D-3L is a standardised instrument for use as a measure of health utility. It is designed for self-completion and is cognitively simple, taking only a few minutes to complete. The EQ-5D-3L is a two-part self-assessment questionnaire. The first part

consists of five items covering five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a five-point Likert scale (no problems, slight problems, moderate problems, severe problems, and extreme problems). Respondents are asked to choose one level that reflects their "own health state today" for each of the five dimensions. Respondents can be then classified into one of 243 distinct health states. The second part is a vertical response scale (EQ-VAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day. EQ-5D-3L health states are converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples.

9. STATISTICAL CONSIDERATIONS

The primary estimand is the difference between mepolizumab 100 mg SC and placebo as add-on treatment in the rate of annualized exacerbations in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels, regardless of IP discontinuation or changes in background medication/starting a prohibited medication, in the absence of COVID-19 pandemic related intercurrent events.

9.1. Statistical Hypotheses

This study is designed to test the superiority of mepolizumab 100 mg SC vs placebo, the significance test will be considered statistically significant at the two-sided 5% alpha level (one-sided 2.5%).

9.2. Sample Size Determination

The primary analysis is based on comparing the annualized rate of moderate/severe exacerbations in participants treated with mepolizumab 100 mg SC vs. placebo.

The null hypotheses used to test the superiority of mepolizumab 100 mg compared to placebo will be:

H_0: $\mu_i = \mu_p$

where μ_i is the annualized exacerbation rate on the mepolizumab 100 mg SC arm and μ_p is the annualized exacerbation rate on the placebo arm.

The (one-sided) alternative hypothesis is that the annualized exacerbation rate is lower on the mepolizumab arm:

H_a: $\mu_i < \mu_p$

The estimated annualized rate of moderate/severe exacerbations in the placebo arm was 1.7 exacerbations (based on exacerbation data observed from studies MEA117113 and MEA117106 [High Stratum], which were conducted prior to the COVID-19 pandemic).

Based on a true population reduction of 23% in the annualized rate of moderate/severe exacerbations following treatment with mepolizumab 100 mg SC compared to placebo, it was estimated that 400 participants per arm (800 participants in total) are required to provide 90% power to detect a statistically significant reduction at the 2-sided 5% level of significance. The smallest observed effect which is predicted to result in a statistically significant difference between mepolizumab 100 mg SC compared to placebo is 15%.

To account for the loss of patient years' data from participants who withdraw early from the trial and no longer provide any data (on- or off-treatment), the sample size includes an additional 44 patients to account for approximately 5.5% of patient-years data being missing, this being the level of missing data encountered in study MEA117113.

The sample size estimate is based on the number of moderate/severe exacerbations per year following a negative binomial distribution [Keene, 2007]. The estimate of 1.7 moderate/severe exacerbations per year in the placebo arm and of 0.55 for the dispersion parameter are based on data observed from studies MEA117113 and MEA117106 (High Stratum). Overall in this study, a total of approximately 800 participants will be randomized with a randomization ratio of 1:1 placebo: mepolizumab 100 mg SC.

Blinded re-evaluations of the sample size will be carried out prior to randomizing the 800th participant to assess whether, based on the overall annualized rate of moderate/severe exacerbations and the level of dispersion seen within the available data, the initial planned sample size of 800 randomized participants would continue to provide 90% power for this study. The sample size re-estimation will follow the method described in [Friede, 2010]. A negative binomial distribution will be fitted to the blinded exacerbations from the available data with participant follow-up time as an offset, and estimates obtained for the overall exacerbation rate and the dispersion (shape) parameter. These estimates will be used to re-calculate the sample size that would be required to provide 90% power. If the re-estimated sample size is less than or equal to the currently planned 800 randomized participants, the study will continue as planned; otherwise the study sample size may be increased to that indicated by the re-estimation, with a potential maximum increase to 1400 participants. Further blinded re-evaluations will be conducted to monitor whether the sample size continues to be appropriate given the emerging event rate. The total sample size will be between 800 as originally planned up to a potential maximum of 1400 participants.

9.2.1. Sample Size Sensitivity

The sample size in Section 9.2 is based on an assumed exacerbation rate of 1.7 exacerbations per year in the placebo group and an expected reduction of 23% in this rate for participants treated with mepolizumab. If the true placebo exacerbation rate or the expected reduction with mepolizumab differ from these assumptions then, at the given sample size, there will be an effect on the power of the study. Table 2 illustrates the effect on the power for the treatment comparison (based on 756 participants, excluding the additional 44 participants to account for early study withdrawals), and a dispersion parameter k=0.55.

Table 2 Effect of placebo rate and expected rate reduction with mepolizumab on the power of the study

% reduction in annualized exacerbation rate with mepolizumab	**Placebo: Annualized Exacerbation Rate**					
	0.9	1.1	1.3	1.5	**1.7**	1.9
	Study Power[a]					
21%	67	73	78	81	84	86
22%	72	77	81	85	87	90
23%	76	81	85	88	**90**	92

a. Power estimate based on a 52-week follow-up for each participant

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Participants Enrolled (ASE)	All participants for whom a record exists on the study database. This population will be used for summarizing reasons for screen and run-in failures.
Modified Intent-to-Treat (mITT)	All randomized participants who receive at least one dose of trial medication. Primary population for analysis of efficacy endpoints data by randomized treatment arm.
Safety	All randomized participants who receive at least one dose of trial medication. Analysis of safety endpoints by actual treatment received for more than 50% of treatment administrations.
Per-Protocol (PP)	All participants in the mITT population not identified as protocol deviators with respect to criteria that are considered to impact the primary efficacy endpoint. Population for supplementary analysis of primary endpoint.

9.3.1. Pharmacokinetics Sub-study

Population	Description
PK	All participants enrolled in the PK sub-study who received at least one dose of trial medication and for whom at least one pharmacokinetic sample was obtained, analysed and was measurable. Population for the PK sub-study analysis.

9.4. Statistical Analyses

All analyses will be carried out using all available data and will be detailed in the Reporting and Analysis Plan (RAP), including details on additional analyses to assess the impact of COVID-19 on this study.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary estimand is defined by the following attributes: Population: Participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels Treatment comparison: Mepolizumab vs. placebo (both as add-on treatment to standard of care) Variable: Number of moderate or severe exacerbations Summary Measure : Ratio of the frequency of exacerbations in the mepolizumab treatment arm to the frequency in the placebo arm. Exacerbation rates will be expressed as an annualized exacerbation rate p.a. Strategies for intercurrent events: A treatment policy strategy will be used for the intercurrent events of discontinuation of study medication, use of medication prohibited by the protocol, and investigational product interruption of 2 or more doses, when these intercurrent events are not associated with disruptions or restrictions imposed due to the COVID-19 pandemic. A hypothetical strategy will be considered when these intercurrent events have occurred as a result of disruptions or restrictions (e.g. lockdown measures, social distancing) imposed due to the COVID-19 pandemic. Full details will be provided in the RAP. The target population for the estimand is as defined by the study inclusion/exclusion criteria and therefore the modified Intent-to-Treat population will be the primary population for efficacy analyses. Participants who prematurely discontinue study treatment (for any reason) will not be required to withdraw from the study and every effort will be made by the

Endpoint	Statistical Analysis Methods
	investigator/site staff to encourage the participant to remain in the study for continued collection of efficacy and safety data. Exacerbations reported by participants from the start of treatment up to the Exit Visit will be included in the primary analysis The primary analysis of the rate of moderate/severe exacerbations will use a negative binomial model, including both on-treatment and, where available, off-treatment exacerbation data. Any remaining missing data will be considered missing at random (MAR). This model will include covariates of smoking status (current vs previous smoker), number of exacerbations in previous year, baseline disease severity (as % predicted post-bronchodilator FEV_1) and geographic region. The rate of moderate/severe exacerbations will be analysed using a negative binomial regression model. Sensitivity analyses to the assumption regarding missing data will be performed using multiple imputation methods based on pattern mixture models. These sensitivity analyses will include an off-treatment imputation approach based on the off-treatment data collected from participants who continue in the study following early discontinuation of randomized treatment and a tipping point analysis. Further details will be provided in the RAP. Full details of the analysis methods to be used will be provided in the RAP.
Secondary	For all secondary endpoints the target population, treatment comparison and strategies for intercurrent events will be the same as for the primary estimand. For the evaluation of the time to the first moderate/severe exacerbation, the summary comparison between treatments will be the hazard ratio. Analysis of this variable will use a Cox's proportional hazards model allowing for covariates of smoking status (current vs previous smoker), number of exacerbations in previous year, baseline disease severity (as % predicted post-bronchodilator FEV_1) and geographic region. Missing values will be considered as censored at random (non-informative censoring). Summaries and graphs of the Kaplan-Meier estimates of the proportion of participants with a moderate/severe exacerbation over time will be produced. The proportion of CAT score responders at Week 52 will be evaluated, and participants with missing values at Week 52 not associated with disruptions or restrictions imposed due to the COVID-19 pandemic on or before the Week 52 visit, will be included in the analysis as a non-responder. Sensitivity analyses to the assumption regarding missing data will be performed using multiple imputation methods based on pattern mixture models. Analysis will be performed using a logistic regression model adjusting for baseline CAT score, smoking status and geographic region. The proportion of SGRQ Total score responders at Week 52 will be evaluated, and participants with missing values at Week 52 not associated with disruptions

Endpoint	Statistical Analysis Methods
	or restrictions imposed due to the COVID-19 pandemic on or before the Week 52 visit, will be included in the analysis as a non-responder. Sensitivity analyses to the assumption regarding missing data will be performed using multiple imputation methods based on pattern mixture models. Analysis will be performed using a logistic regression model adjusting for baseline SGRQ total score, smoking status and geographic region. The proportion of E-RS: COPD responders at Week 52 will be evaluated, and participants with missing values at Week 52 not associated with disruptions or restrictions imposed due to the COVID-19 pandemic on or before the Week 52 visit, will be included in the analysis as a non-responder. Sensitivity analyses to the assumption regarding missing data will be performed using multiple imputation methods based on pattern mixture models. Analysis will be performed using a logistic regression model adjusting for baseline score, smoking status and geographic region. The estimand for exacerbations that resulted in an ED visit or hospitalization will be the same as for the primary endpoint and analysis will use the same methods as for the primary endpoint.
Other	See Section 3 for a list of all other endpoints. Full details of any analyses to be performed on these endpoints will be provided in the RAP.

The treatment comparison of interest for the primary and secondary endpoints is mepolizumab 100 mg SC vs placebo in the mITT population. A hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a step-down closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy.

For example, for the primary endpoint, mepolizumab will be compared to placebo at a two-sided α=0.05 (one-sided α=0.025). The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the one-sided 2.5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualized rate of moderate/severe exacerbations (primary endpoint)

2. Time to first moderate/severe exacerbation

3. Proportion CAT [Jones, 2009] score responders at Week 52

4. Proportion of SGRQ [Meguro, 2007] Total score responders at Week 52

5. Proportion of E-RS: COPD responders at Week 52 [Leidy, 2011; Leidy, 2014; [E-RS™: COPD, 2016]

6. Annualized rate of exacerbations requiring ED and/or hospitalization

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Summaries of data will include data from scheduled assessments only, all data will be reported according to the nominal visit for which it was recorded (i.e. no visit windows will be applied). Data from unscheduled visits will be included in "overall" and "any post-Baseline" summaries. Further details will be provided in the RAP.

9.4.2.1. Extent of Exposure

The number of participants administered interventional product, the number of treatments administered, and the number of days over which treatment was administered will be summarised.

9.4.2.2. Adverse Events

Adverse Events will be coded using the standard GlaxoSmithKline MedDRA and will be grouped by system organ class (SOC). AEs will be summarised by frequency and percentage of participants, by SOC and preferred term within each treatment group. Separate summaries will be presented for all AEs, drug-related AEs, SAEs, AE's leading to permanent discontinuation of interventional product or withdrawal from study, any AEs of special interest and adjudicated events.

9.4.2.3. Clinical Laboratory Evaluations

Hematology (including blood eosinophils) and clinical chemistry data will be summarized at each scheduled assessment. The proportion of values outside of the normal reference range and those meeting the criteria for potential clinical significance will also be summarised. Further details will be provided in the RAP.

9.4.2.4. Other Safety Measures

Other scheduled safety assessments such as vital signs data (including pulse rate, systolic and diastolic blood pressure) and ECG data (including categorised QTcF values) will be summarized at each scheduled assessment. Further details will be provided in the RAP.

9.4.2.5. Immunogenicity

Immunogenicity data related to the presence of antibodies to mepolizumab will be summarised using appropriate descriptive statistics. Further details will be provided in the RAP.

9.4.3. Other Analyses

9.4.3.1. Health Related Quality of Life and Health Outcomes

Details of the summary of additional health related quality of life and health outcomes related data will be given in the RAP.

9.4.3.2. Pharmacodynamic Analyses

Blood eosinophils ratio to Baseline will be analysed using mixed model repeated measures adjusting for Screening, smoking status, geographic region, visit by Screening interaction and visit by treatment group interaction. Data will be log-transformed ($\log_e$) prior to analysis.

9.5. Interim Analyses

No formal interim analyses of efficacy data are planned for this study. See Section 9.2.1 for details regarding blinded sample size evaluation.

9.5.1. Data Monitoring Committee (DMC)

Not applicable

9.6. Pharmacokinetics Analyses (PK Sub-study)

For participants included in the PK sub-study, blood samples will be collected to determine mepolizumab plasma concentrations at visits specified in the SoA table (Section 1.3). Sparse blood sampling is being implemented in this PK sub-study. Mepolizumab plasma concentrations will be evaluated by population PK methods using the established population PK model developed based on previous mepolizumab data collected during mepolizumab clinical development. The analysis will be conducted using appropriate software and will provide individual predicted plasma concentrations as well as individual predicted post-hoc apparent clearance estimates from which potential ethnic differences in mepolizumab exposure between Chinese participants in China and non-Asian participants in the US will be explored using a confidence interval approach. Evaluation of similarity in exposure will be guided by the confidence interval excluding at least a two-fold difference. If deemed necessary population PK parameter estimates for the Chinese population will be estimated.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively by group. Further details will be provided in the separate PK sub-study RAP. The PK sub-study results will be reported separately from the main CSR.

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 and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented 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.
- In rare instances and with agreement from the Medical Monitor following consultation, a participant can be rescreened. In such circumstances, they are required to sign a new ICF.
- Participants who enrolled in the study prior to Protocol Amendment 6 implementation and who have agreed to extend study participation beyond 52 weeks must re-sign a new ICF at, or prior to, the completion of the Week 52 Visit (Exit Visit 15).

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. 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.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the 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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- 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 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

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

10.1.8. 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

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not

as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

10.2. Appendix 2: Anaphylaxis Criteria

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 hrs) 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., dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

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

3) 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

Reference

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson Jr FN, Bock AS, Branum A et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391-3

10.3. Appendix 3: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the central laboratory

Local laboratory results are only allowed for parasitic screening. The investigator should decide what type of laboratory test, if any, is necessary.

- 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.
- Pregnancy testing (urine) be conducted prior to each dose of study intervention and at Study Exit/Early Withdrawal Visit (4 weeks after the last dose). Note that for female participants pregnancy occurring within 16 weeks after the last dose should be reported.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cells (RBC) Count Hemoglobin Hematocrit Red Cell Distribution Width (RDW) Mean Platelet Volume (MPV)	RBC Indices: MCV MCH	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT) International normalized ratio (INR)	Total and direct bilirubin

Laboratory Assessments	**Parameters**			
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting]	Calcium	Alkaline phosphatase	Albumin [3]
Other Screening Tests	• total IgE • Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • Parasitic Screening (only required in countries with high-risk or for participants who have visited high-risk countries in the past 6 months). Sites should **use local laboratories.**			

NOTES:
1. Details of liver chemistry stopping criteria (Section 7.1.1) and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 7. 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, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. **China and US only:** For participants participating in the PK sub-study Albumin will be tested at Visit 2 only

After randomization to end of study neither the site staff nor GSK personnel will be sent results from the central laboratory for absolute and differential values for eosinophils, lymphocytes, basophils, neutrophils and monocytes, until the study has been unblinded. However, sites will be sent total white blood counts throughout the study.

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 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.

10.4.2. 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:

- Results in death
- 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. (See Section 7.1 and Appendix 7 for additional events defined as SAEs).

10.4.3. 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

10.4.4. 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 AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

10.4.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

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

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **Medical Monitor.**

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SRM.

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

10.5.1. 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 enrollment.

10.5.2. 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[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• 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 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. 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)

10.5.3. 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 and up to 16 weeks after the last dose of study intervention.
- 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 for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) 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 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study intervention

10.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

China only: No genetic samples will be collected from participants in China.

- Genetic variation may impact a participant's response to treatment, susceptibility, severity and progression of disease. Variable response to mepolizumab may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.

- DNA samples will be used for research related to mepolizumab in COPD. CCI [redacted]
- CCI [redacted].
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on mepolizumab for the treatment of COPD continues but no longer than 15 years after the last participant last visit or other period as per local requirements

10.7. Appendix 7: Liver Safety: Required Actions, Monitoring and Follow-up Assessments

Liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1], [2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions, Monitoring and Follow up Assessments	
Actions	**Follow Up Assessments**
• 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 (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment since restart/rechallenge is not allowed per protocol. Permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, within 4 weeks after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia This blood sample will be sent to the central laboratory to maintain the blind while study is ongoing. Results will be provided only if unblinding of a participant's

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 hours** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • 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 hours** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	treatment assignment is required. Also note that the mechanism of action of mepolizumab leads to lowering of eosinophils. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • 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]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy 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 INR 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. In those with underlying chronic hepatitis B at study entry quantitative hepatitis B DNA and hepatitis delta antibody. 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].
5. PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

References

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

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P 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.

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 • 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.

10.8. Appendix 8: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

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

10.8.1. Definition of Medical Device AE and ADE

Medical Device Incident Definition
• An AE is any untoward medical occurrence, in a clinical study participant, or other persons e.g., Investigator, study site staff, nurse etc., temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. • An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event **that:**
a. Led to death b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the benefit/risk assessment (see Section 2.3).

10.8.3. Definition of Device Deficiency

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

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

AE, SAE and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK/AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

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

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

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

Follow-up of AE/SAE/device deficiency

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

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.8.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool

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

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the GSK medical monitor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in SRM.

10.8.6. Reporting of SADEs

SADE Reporting to GSK
NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for SAE reporting can be found in SRM.

10.9. Appendix 9: Country-specific Requirements

Participants in China will not participate in the genetic (Appendix 6) or biomarker (Section 8.8) research.

Serious AEs (Section 8.3) in China will be recorded from the time the informed consent form is signed until the Exit Visit/Study Withdrawal Visit at the time points specified in the SoA (Section 1.3).

In China, the Centre of Drug Evaluation (CDE) requested the inclusion in the protocol of a PK sub-study to assess potential ethnic differences in the PK of mepolizumab 100 mg in liquid formulation, administered subcutaneously by a safety syringe, between Chinese and non- Chinese participants. Therefore, a PK sub-study comparing Chinese participants in China with non-Asian participants in the US was included.

10.10. Appendix 10: COVID-19 Measures

10.10.1. Overall Rationale For This Appendix

The COVID-19 pandemic may impact the conduct of this study. Challenges may arise from disruptions or restrictions imposed due to the COVID-19 pandemic (e.g., from quarantines, site closures, travel limitations, interruptions to the supply chain for the interventional product or from other considerations such as if site personnel or study participants become infected with COVID-19). These challenges may lead to difficulties in meeting protocol-specified procedures, including administering the interventional product, or adhering to protocol-mandated clinic visits and laboratory testing.

This protocol appendix outlines measures that are applicable for sites and participants when clinic visits are impacted by the COVID-19 pandemic special circumstances. This appendix applies to study Visit 5 and onwards. 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.

10.10.2. 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 5 and onwards for participants unable to attend a site visit due to COVID-19 related restrictions. For such visits every effort should be made to adhere to protocol-specified assessments and procedures. Missing protocol data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

10.10.2.1. 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 a 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. See the SRM for details.

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 COPD 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 is responsible for administering the study IP (at the discretion of the investigator) according to procedures detailed in the protocol. See Section 6, Study Intervention and the pharmacy manual in the SRM.

Study assessments performed through home healthcare

All assessments from Visit 5 and onwards stated in the SoA tables in Section 1.3.1 and 1.3.2 can be performed through home healthcare with the exception of the Exit Visit, and the below procedures, which must be performed in clinic:

- Pre-bronchodilator spirometry;
- Clinician rated response to therapy; and
- Physical examinations

10.11. Appendix 11: Protocol Amendment History

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

The overall rationale and the summary of changes tables for previous amendments are listed below.

Amendment 1-USA-1: 23-May-2019

Overall Rationale for Amendment 1-USA-1:

Amendment 1-USA-1 was created to include an optional pharmacokinetic (PK) sub-study to assess potential ethnic differences in the PK of mepolizumab 100 mg in liquid formulation, administered subcutaneously by a safety syringe, between non-Asian participants in the US and Chinese participants in China. Summary of changes are described in the table below.

Section # and Name	Description of Change	Brief Rationale
Synopsis	Added information that an optional PK sub-study is included	Align the Synopsis with the rest of the protocol
Section 1.3: Schedule of activities	Updated Section to include informed consent for the PK sub-study and schedule of PK blood samples collection	To align the schedule of activities with other Sections of protocol
Section 3: Objectives and endpoints	Added the PK sub-study objectives and endpoints	Assess potential ethnic differences in PK between non-Asian participants in the US and Chinese participants in China.
Section 4: Overall design	Added information that an optional PK sub-study is included	Explain that a PK sub-study is included in the study design
Section 7.2: Participant Discontinuation/Withdrawal from the Study	Added information that a PK sample will be collected at the IP Discontinuation and Withdrawal Visits	Provide clarity on collection of PK sample
Section 8.5: Pharmacokinetics	Added a pharmacokinetic section to describe PK samples collection, samples analysis and assay method	Provide clarity and information on the PK sub-study.
Section 9.3.1:	Added information about the PK population	Provide information on the PK population to be analysed

Section # and Name	Description of Change	Brief Rationale
Synopsis	Added information that an optional PK sub-study is included	Align the Synopsis with the rest of the protocol
Section 1.3: Schedule of activities	Updated Section to include informed consent for the PK sub-study and schedule of PK blood samples collection	To align the schedule of activities with other Sections of protocol
Pharmacokinetics sub-study		
Section 9.4.3.3: PK analyses	Added description of the PK data analysis	Provide information on the PK analysis
Appendix 3: Clinical laboratory tests, Table 3	Added Albumin to the clinical chemistry tests	Clarify that Albumin test is a required test for the PK sub-study only

Amendment 2-CHI-1: 23-May-2019

Overall Rationale for Amendment 2-CHI-1:
This protocol amendment was created to include an optional pharmacokinetic (PK) sub-study to assess potential ethnic differences in the PK of mepolizumab 100 mg in liquid formulation, administered subcutaneously by a safety syringe, between non-Asian participants in the US and Chinese participants in China.

Section # and Name	Description of Change	Brief Rationale
Synopsis	Added information that an optional PK sub-study is included in the protocol	Align the Synopsis with the rest of the protocol
Section 1.3: Schedule of activities (SoA)	Updated Section to include: Informed consent for the PK sub-study and schedule of PK blood samples collection Deleted row for the genetic informed consent Deleted rows for the collection of biomarker and genetic samples	To align the schedule of activities with other Sections of protocol
Section 3: Objectives and endpoints	Added the PK sub-study objectives and endpoints	Assess potential ethnic differences in PK between non-Asian participants in the US and Chinese participants in China.
Section 4: Overall design	Added information that an optional PK sub-study is included	Explain that a PK sub-study is included in the study design
Section 7.2: Participant Discontinuation/Withdrawal from the Study	Added information that a PK sample will be collected at the IP Discontinuation and Withdrawal Visits	Provide information on collection of PK samples
Section 8: Study assessments and procedures	Deleted text related to the genetic consent form and sample	Ensure consistency of the protocol As genetic samples are not collected from Chinese participants
Section 8.3.1: Time period and frequency for collecting AE and SAE Information	Added text to clarify that SAEs will be collected from the time of signing the informed consent	To comply with specific requirements for China

Section # and Name	Description of Change	Brief Rationale
Section 8.5: Pharmacokinetics	Added a pharmacokinetic section to describe PK samples collection, samples analysis and assay method	Provide clarity and information on the PK sub-study.
Section 8.7: Genetics	Deleted text from Section	Provide information that genetic samples are not collected from Chinese participants
Section 8.8: Biomarkers	Deleted text from Section	Provide information that biomarker samples are not collected from Chinese participants
Section 9.3.1 Pharmacokinetics sub-study	Added information about the PK population	Provide information on the PK population to be analysed
Section 9.4.3.3: PK analyses	Added description of the PK data analysis	Provide information on the PK analysis
Appendix 3: Clinical laboratory tests, Table 3	Added Albumin to the clinical chemistry tests	Clarify that Albumin test is a required test for the PK sub-study only
Appendix 6: Genetics	Deleted text related to genetic test	Ensure consistency of the protocol
Section 10.9: Country-specific requirements	Added information on China specific requirements	Ensure consistency with the protocol

Amendment 3: 18-Jul-2019

Overall Rationale for Amendment 3:

This protocol amendment was created to make changes to Study design; integration of protocol amendment 1-USA-1 and protocol amendment 2-CHI-1 including a pharmacokinetics sub-study in China and the US; correction of typographical errors. Protocol changes are described in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis	Removed requirement of ≥300 cells/µL in the 12 months prior Screening Visit 1 Updated the number of screened participants to approximately 1600 Added information that number of participants may increase to 1000 maximum after sample size re-evaluation Added information about PK sub-study in China and the US only	Align the synopsis with the rest of the protocol Align the synopsis with Section 9: Statistics Integrate country specific amendment for China and the US into this global amendment
Section 1.2: Schema	Changed Pre-screening Visit to Screening Visit 0	Align Schema with other Sections of the protocol
Section 1.3: Schedule of activities (SoA)	Updated Section to include: Re-naming the Pre-screening Visit 0 to Screening Visit 0 Provided details on the hematology test at Screening Visit 0 Added PK informed consent and scheduled PK sample collection Removed post-bronchodilator Spirometry during the intervention period Clarified that no genetic or biomarker samples will be collected from participants in China. Update the SoA foot-note	Align Section with study design and other Sections of protocol Align with the changes in the SoA
Section 3: Objectives and endpoints	Other endpoints: Removed post-bronchodilator spirometry Added the PK sub-study objectives and endpoints	Change in study design Integrate China and the US country specific amendment into this global amendment

Section # and Name	Description of Change	Brief Rationale
Section 4: Study design	Added requirement for eosinophil count of ≥300 cells/µL at Screening Visit 0. Removed historical requirement of ≥300 cells/µL in the 12 months prior Screening Visit 1. Clarified that number of participants may increase to 1000 maximum after sample size re-evaluation Added information about PK sub-study in China and the US	Change in study design Alignment with the statistical Section
Section 5.1: Inclusion criteria	Added a new inclusion criterion: Blood eosinophil count of ≥300 cells/µL from the hematology sample collected at Screening Visit 0. Changed predicted FEV_1 reference range from Quanjer to NHANES III	Change in study design
Section 5.2: Exclusion criteria	Further clarified that Participants with a past history or concurrent diagnosis of asthma are excluded regardless of whether they have active or inactive disease.	Further clarification of exclusion criterion 1
Section 5.4: Screen and Run-in failures	Clarified that re-screening of participants is permitted only after written approval to proceed with re-screening from the Medical Monitor	Clarification about re-screening
Section 8: Study assessments and procedures	Updated Section in alignment with SoA Section 1.3. Added text in Section 8.3.1 to clarify that in China SAEs will be collected from the time of signing the informed consent	To comply with specific requirements for China

Section # and Name	Description of Change	Brief Rationale
Section 8.5: Pharmacokinetics	Added a pharmacokinetic section specific to China and the US, to describe PK samples collection, samples analysis and assay method.	Provide clarity and information on the PK sub-study.
Sections 8.7: Genetics and 8.8: Biomarkers	Clarified that genetic and biomarker samples will not be collected from participants in China.	To comply with specific requirements for China
Section 9.3.1: Pharmacokinetics sub-study	Added information about the PK population	Provide information on the PK population to be analysed
9.6: Pharmacokinetics Analyses (PK Sub-study)	Added Section to describe analysis of the PK sub-study.	
Appendix 3: Clinical laboratory tests, Table 3	Added Albumin to the clinical chemistry tests	Clarify that Albumin test is a required test for the PK sub-study in China and the US only
Appendix 6: Genetics	Clarified that no genetic samples will be collected from participants in China	Integrate China country specific amendment in this global amendment
Section 10.9: Country-specific requirements	Added information on China specific requirements	Ensure consistency with the protocol
Appendix 10: protocol amendment history	Added Appendix to describe protocol amendment history for China and the US	Describe country specific protocol amendment for China and the US

Amendment 4: 13-Sep-2019

Overall Rationale for Amendment 4:
This protocol amendment was created to make changes to Study design and correct some typographical errors. Protocol changes are described in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.1: synopsis	Added information that based on the results from the 2 previously completed COPD studies and feedback from health authorities, the study patient population must have a documented historical blood eosinophil count of ≥150 cells/µL in the 12 months prior to Screening Visit 0 and a blood eosinophil counts of ≥300 cells/µL at Screening Visit 0. Participants with no documented historical blood eosinophil count of ≥150 cells/µL must meet this threshold at the Screening Visit 1 assessment Clarified that participants must have at least 2 COPD exacerbations that were treated with systemic corticosteroids with or without antibiotics, or 1 severe exacerbation requiring hospitalization in the 12 months prior to Screening Visit 1 The number of participants estimated to be screened is 2286	Clarify change in study design
Section 1.2: Schema	The duration between Visit 0 and Visit 1 was changed to >14 days. Footnote was updated	Ensure consistency with other Sections of the protocol
Section 1.3: Schedule of activities	Updated Section to increase the duration between Visit 0 and Visit 1 to >14 days. Added a row for historical blood eosinophil count Updated foot note to clarify that only participants with no historical eosinophil count in the 12 months prior Screening Visit 0 will have a hematology sample collected at Screening Visit 1. Clarified that where several historical blood eosinophil counts are obtainable, the highest eosinophil count not associated with a COPD exacerbation should be recorded in the eCRF for each of the following specified periods: ≥1 to <6 months and 6 to 12 months. In order to meet the Inclusion Criteria #2 (Section 5.1), a historical blood eosinophil measurement must	Ensure alignment with the protocol

Section # and Name	Description of Change	Brief Rationale
	meet the following: It must have been measured between 12 months and 1 month prior to Visit 0 and it must not have been measured within 14 days of a COPD exacerbation. If, in either of the 2 specified periods, the only historical documented blood eosinophil count is associated with a COPD exacerbation, then this eosinophil count cannot be used for inclusion in the study but should be recorded in the eCRF	
Section 2.1: Study rationale	Updated Section to clarify that to ensure stability of eosinophil counts participants must have 2 eosinophil measurements. One historical and one at Screening Visit 0. Participants with no documented historical eosinophil count of ≥150 cells/µL must meet this threshold at the Screening Visit 1 assessment	Clarified rationale for the requirement of 2 blood eosinophil measurements
Section 4.1: Overall design	Added information that participants must also have a documented historical eosinophil count of ≥150/µL in the 12 months prior to Screening Visit 0 and historical eosinophil count must not have been measured during a COPD exacerbation. Participants with no documented historical eosinophil count of ≥150 cells/µL must meet this threshold at the Screening Visit 1 Clarified that participants must have at least 2 moderate COPD exacerbations that were treated with systemic corticosteroids (intramuscular (IM), intravenous, or oral) with or without antibiotics, or 1 severe exacerbation requiring hospitalization in the 12 months prior to Screening Visit 1	Clarify changes in study design and ensure alignment with other Sections of the protocol
Section 4.2: Scientific rationale for study design	Clarified that duration between Screening V0 and Screening V1 was increased to >14 to allow a repeated measurement of eosinophil count at Visit 1	Ensure alignment with other Sections of protocol

Section # and Name	**Description of Change**	**Brief Rationale**
Section 5.1: Inclusion Criteria	Updated Inclusion Criteria # 2: Participants must have: A peripheral blood eosinophil count of ≥300 cells/µL from the hematology sample collected at Screening Visit 0 and a documented historical eosinophil count of ≥150/µL in the 12 months prior to Screening Visit 0 that was measured between 12 months and 1 month prior to Visit 0, and that was not measured within 14 days of a COPD exacerbation. Participants with no documented historical blood eosinophil count of ≥150 cells/µL must meet this threshold at the Screening Visit 1 Updated inclusion criterion # 5: Two or more moderate COPD exacerbations that were treated with systemic corticosteroids (intramuscular (IM), intravenous, or oral) with or without antibiotics etc.	Change in study design to include 2 blood eosinophil counts, one historical and one at Screening
Section 5.3.1: Randomization inclusion criteria	Added a new Randomization inclusion criterion: Participants that do not have a historical blood eosinophil count that satisfies screening Inclusion Criterion 2 (Section 5.1) must have a Screening Visit 1 blood eosinophil count ≥150 cells/µL	Alignment with other Sections of protocol
Section 8: Study assessments and procedures; critical procedures performed at Screening Visit	Further emphasized that in case several historical eosinophil counts are obtainable, the highest eosinophil count should be recorded in the eCRF for each of the following periods: ≥1 to <6 months and 6 to12 months. In addition, to satisfy the inclusion criterion #2, a historical blood eosinophil measurement must meet the following: It must have been measured between 12 months and 1 month prior to Visit 0 and it must not have been measured within 14 days of a COPD exacerbation. Clarified that a hematology sample is only collected at Screening Visit 1 for participants who do not have a historical eosinophil count meeting the Inclusion Criteria	Alignment with Section 1.3
Typographical errors	IVRS changed to IWRS throughout the protocol. Other typographical errors were corrected.	

Amendment 5: 16-OCT-2020

Overall Rationale for Amendment 5

This protocol amendment was created to make changes to the study following the COVID-19 pandemic, to introduce home healthcare to perform study assessments, update details of the primary estimand and strategies for handling intercurrent events, add clarity to some sections of the protocol, and to correct typographical errors and inconsistencies. Protocol changes are described in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis	Added text related to home healthcare Updated the approximate number of participants to be screened	Clarify that home healthcare is included in the study as mitigation during COVID-19 restrictions Updates based on observed screen failure rate
Section 1.2: Schema	Updated the range of days for Visit 0 and Visit 1 to align with Section 1.3	Ensure consistency between Sections
Section 1.3: Schedule of activities (SoA)	Updated SoA, removed study day and study week Updated the number of days between V0 and Visit 1 Updated medical history to include Hepatitis B and C and COVID-19 Removed Hepatitis B and C tests from SoA Removed collection of used rescue medication Updated footnotes to add clarity.	Ensure Clarity and consistency across the SoA Align with new GSK guidance on Hepatitis B and C testing

Section # and Name	**Description of Change**	**Brief Rationale**
Section 4.1: Study design	Added text related to home healthcare	Clarify that home healthcare is included in the study as mitigation during COVID-19 restrictions
	Updated the approximate number of participants to be screened	Updates based on observed screen failure rate
Section 5.1: Inclusion Criteria	Inclusion criterion 5: Added a note related to COVID-19 and COPD exacerbations	Clarify that COPD exacerbations related to COVID-19 infection must not be counted as COPD exacerbations for inclusion in the study
Section 5.2: Exclusion criteria	Criterion no.7: Added a note to clarify that where a single ECG demonstrates a prolonged QTcF interval at Screening, two more ECG readings should be obtained with the average of the triplicate QTcF measurements used to determine eligibility	Provide clarity about ECG at Screening
	Criterion no.14: Deleted "(-e.g., presence of hepatitis B surface antigen [HbsAg] or positive hepatitis C antibody test result)".	Deleted sentence related to hepatitis B and C
	Added a new exclusion criterion (no.24) related to COVID-19	Provide information related to COVID-19 Exclusion.

Section # and Name	Description of Change	Brief Rationale
Section 5.3.2: Randomization exclusion criteria	Added a new randomization exclusion criterion (no.5) related to COVID-19.	Provide information related to COVID-19 Exclusion.
Section 5.4: Screen and run-in failures	Updated Section to clarify the information collected at Screening Visit 0 and Screening Visit 1.	Add clarity to protocol.
Section 6.1: Study intervention(s) administered	Updated Table 1 to include the correct excipients of interventional product, mepolizumab and placebo.	Provide correct information on interventional product.
Section 6.4: Study intervention compliance	Added text to clarify that where applicable study assessments and study intervention can be performed through home healthcare.	Provide information on home healthcare.
Section 6.5.2: Permitted medications and non-drug therapies	Added BIPAP as a permitted therapy. Removed monoclonal antibodies to align with exclusion criterion no.18.	Ensure consistency across Sections of the protocol.
Section 6.5.3: Prohibited medications and non-drug therapies	Clarified that morning COPD medications should be withheld at all visits where spirometry is performed. Clarified that monoclonal antibodies and chronic oral corticosteroids for non-COPD treatment are not permitted.	Provide clarity on prohibited medications.
Section 7.1.1: Liver chemistry stopping Criteria	Included minor revision to align with new protocol template.	Align with new protocol template
Section 8: Study assessments and procedures	Added text to clarify that where applicable study assessments can be performed through home healthcare.	Provide information on home healthcare
Section 8.2.3: Electrocardiogram	Updated information about ECG recordings.	Provide flexibility for ECG recording
Section 8.3.7: Medical device deficiencies	Updated Section to align with new protocol template and new regulatory requirements for reporting device deficiencies.	Alignment with new protocol template.
Section 8.7: Genetics	Deleted the following sentence: In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the	Clarify that a replacement genetic sample

Section # and Name	**Description of Change**	**Brief Rationale**
	participant. Signed informed consent will be required to obtain a replacement sample.	will not be requested.
Section 9: Statistical Considerations	Updated details of the primary estimand.	Clarify handling of issues related to the COVID-19 pandemic
Section 9.4.1: Efficacy Analysis	Updated details of attributes of the primary estimand, as well as intercurrent events and strategies for handling intercurrent events.	Clarify handling of issues related to the COVID-19 pandemic
Section 10.7 Appendix 7: Liver Safety	Deleted hepatitis B surface antigen as it is no longer applicable. Included minor revision to align with new protocol template.	Align with other sections of protocol
Section 10.8 Appendix 8: Device deficiency	Updated Section to align with new protocol template and new regulatory requirements for reporting device deficiencies.	Alignment with new protocol template
Section 10.10: Appendix 10: COVID-19 Measures	Added Appendix 10: COVID-19 Measures, to inform about home healthcare during the COVID-19 pandemic. Added Table 4 to clarify the study assessments that can be performed through home healthcare.	Provide information on home healthcare
Other Protocol Sections	Minor updates are made throughout the protocol to provide clarity and consistency.	Provide clarity and consistency

10.12. Appendix 12: Abbreviations and Trademarks

LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
ADE	Adverse Device Effect
AE	Adverse Event
AECOPD	Acute exacerbations of COPD
ALT	Alanine aminotransferase
ASE	All participants enrolled population
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BP	Blood pressure
BIPAP	Bilevel Positive Airway Pressure
CAT	COPD Assessment Test
CIOMS	Council for International Organizations of Medical Sciences
CEC	Clinical endpoint committee
COA	Clinical Outcomes Assessment
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease
CPK	Creatine phosphokinase
CPAP	Continuous positive airway pressure
CSR	Clinical Study Report
CRF	Case Report Form
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiography
eCRF	Electronic case report form
ED	Emergency department
eDiary	Electronic diary
EDTA	Ethyl enediamine tetra acetic acid
EGPA	Eosinophilic Granulomatosis with Polyangitis
EQ-5D-3L	EuroQol questionnaire
EQ-VAS	EuroQol-Visual Analogue Scale
E-RS: COPD	Evaluating Respiratory Symptoms in COPD
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FAAN	Food Allergy and Anaphylaxis Network
FEV_1	Forced expiratory volume in one second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCSP	GSK's Global Clinical Safety and Pharmacovigilance group
GSK	GlaxoSmithKline
hCG	Human chorionic gonadotropin
HbsAg	Hepatitis B surface antigen

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HPCL	High performance liquid chromatography
HRQoL	Health related quality of life
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IEC	Independent ethics committee
IgG	Immunoglobulin G
IL	Interleukin
IP	Interventional Product
IM	Intramuscular
INR	International normalized ratio
IP	Interventional Product
IRB	Institutional research board
IV	Intravenous
IWRS	Interactive Web Response System
IDFU	Instruction Direction For Use
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LABA	Long acting $beta_2$-agonist
LAMA	Long acting muscarinic antagonist
LDH	Lactate dehydrogenase
LFT	Liver function testing
LRTI	Lower Respiratory Tract Infection
LTOT	Long term oxygen therapy
MACE	Major Adverse Cardiovascular Event
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MI	Myocardial infarction
mITT	Modified Intent-to Treat
mL	Millilitre
mMRC	Modified Medical Research Council Grading System
MSDS	Materials Safety Data Sheet
NAb	Neutralizing Antibody
NHANES	National Health and Nutrition Examination Survey
NIAID	National Institute of Allergy and Infectious Disease
NIMP	Non-interventional Medicinal Product
NYHA	New York Heart Association
PK	Pharmacokinetic
PD	Pharmacodynamic
PDE-4	Phosphodiesterase-4
PEF	Peak expiratory flow

PGx	Pharmacogenetics
PI	Principal Investigator
PP	Per protocol
prn	As needed
PRO	Patient reported outcomes
QTcF	QT interval corrected with Fridericia's formula
RAP	Reporting and analysis plan
RBC	Red blood cells
SABA	Short acting $beta_2$-agonist
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAMA	Short acting muscarinic antagonist
SaO2	Oxygen Saturation
SC	Subcutaneous
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SGRQ	St. George's Respiratory Questionnaire
SGRQ-C	St. George's Respiratory Questionnaire for COPD
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class
SS	Safety syringe
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
ULN	Upper limit of normal
US	United States
USADE	Unanticipated Serious Adverse Device Effect
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
CAT

Trademarks not owned by the GlaxoSmithKline group of companies
EQ-5D-3L
E-RS-COPD
EXACT
MedDRA

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