Protocol Amendment 4

Study ID: 201536

Official Title of Study: A randomized, double blind, parallel group study of the efficacy and safety of Mepolizumab as adjunctive therapy in patients with severe asthma with eosinophilic inflammation

NCT number: NCT03562195

Date of Document: 18-NOV-2021

TITLE PAGE

Protocol Title: A randomized, double blind, parallel group study of the efficacy and safety of Mepolizumab as adjunctive therapy in patients with severe asthma with eosinophilic inflammation

Protocol Number: 201536/04

Compound Number: SB-240563

Study Phase: III

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Sponsor Name and Legal Registered Address:

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N197489_00	2018-MAR-28	Original
2014N197489_01	2018-NOV-30	Amendment No. 1
This protocol amendment is being implemented to update Medical Monitor Name and Contact Information, clarify inclusion criteria/exclusion criteria, randomization criteria, withdrawal/stopping criteria, subject and study completion, concomitant therapy, efficacy assessments and other minor protocol clarifications.		
2014N197489_02	2019-MAY-17	Amendment No. 2
This protocol amendment is being implemented to update inclusion criteria 3#, switching FEV1 predicted value equation from NHANESIII to Quanjer, 2012, updated related content in pulmonary function testing section, reference and abbreviation accordingly.		
2014N197489_03	2019-OCT-01	Amendment No. 3
This protocol amendment is being implemented to update Secondary Medical Monitor Name and Contact information, clarify eDiary objective assessment links to clinically significant exacerbation and update the wordings about the blinded evaluation of exacerbation.		
TMF-11823581	2021-NOV-18	Amendment No. 4
This protocol amendment is being implemented to update Medical Monitor Name and Contact information, clarify type of exacerbation in some other endpoints related to systemic corticosteroids (SCS) usage and unscheduled healthcare resource utilization, added “mean days of work/school missed” as an other endpoint, updated analysis in synopsis, Updated the study day of V2-1 and V2-2 in Schedule of Activities table, updated time period for collecting SAE information, added population PK analysis as an optional approach for mepolizumab concentration data analysis. Due to the impact of pandemic and observed lower event rates under blind assessment, updated statistical consideration section and changed analysis methods to borrow data from MEA115588, and added a statistical appendix.		

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Medical Monitor Name and Contact Information

Role	Name	email address	Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	PPD	PPD	PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China
Secondary Medical Monitor	PPD	PPD	PPD	PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China
SAE		PPD		PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China

Regulatory Agency Identifying Number(s): NA

SPONSOR SIGNATORY

Protocol Title: A randomized, double blind, parallel group study of the efficacy and safety of Mepolizumab as adjunctive therapy in patients with severe asthma with eosinophilic inflammation

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Robert Chan, MD Project Physician Lead, Clinical Development Group Director, Respiratory TAU	**Date**

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A randomized, double blind, parallel group study of the efficacy and safety of Mepolizumab as adjunctive therapy in patients with severe asthma with eosinophilic inflammation

Rationale:

This study proposed to be conducted in China is similar in design to the global pivotal study MEA115588 which has established favourable benefit risk profile of mepolizumab in severe asthmatics with eosinophilic inflammation. While patients with severe asthma represent only a small percentage (5-10%) of the asthmatic population, they incur the greatest direct costs for the treatment of asthma. Current asthma treatment guidelines offer minimal options for the severe asthmatic patient on intensive therapy with frequent exacerbations. There is a significant unmet medical need to provide better treatment options for this segment of the asthma population. Previous studies in severe asthmatic patients with eosinophilic inflammation have demonstrated a reduction in the frequency of clinically significant exacerbations and a reduction in oral corticosteroids (OCS) in OCS-dependent subjects with mepolizumab which has also exhibited a favorable safety profile. This study is a Phase III study in Chinese population, to evaluate the efficacy and safety of mepolizumab in severe asthmatics with eosinophilic airway inflammation.

Objectives and Endpoints:

Objectives	Endpoints
Primary Efficacy	
• To evaluate the efficacy of mepolizumab 100 mg subcutaneous (SC) every 4 weeks versus placebo on the frequency of clinically significant exacerbations in adult and adolescent Chinese subjects with severe asthma with eosinophilic airway inflammation.	Frequency of clinically significant exacerbations of asthma over the 52-week treatment period. Clinically significant exacerbations are defined as: Worsening of asthma which requires use of systemic corticosteroids (SCS)[1] and/or hospitalizations and/or Emergency Department (ED) visits. *[1]For all subjects, i.v. or oral corticosteroid for at least 3 days or a single IM Corticosteroid (CS) dose is required. For subjects on maintenance systemic corticosteroids (SCS), at least double the existing maintenance dose for at least 3 days is required.*
Secondary Efficacy	
• To evaluate the effects of mepolizumab compared with placebo on a range of clinical markers of asthma control,	1. Time to first clinically significant exacerbations 2. Mean change in St. George's Respiratory Questionnaire (SGRQ) at Week 52

Objectives	Endpoints
including exacerbations, lung function, and quality of life.	3. Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits over the 52-week treatment period 4. Frequency of exacerbations requiring hospitalisation over the 52-week treatment period 5. Mean change from baseline in clinic pre-bronchodilator FEV1 at Week 52
Safety	
• To evaluate the safety and tolerability of mepolizumab compared with placebo, in subjects with severe asthma with eosinophilic inflammation	1. Adverse Event including systemic (i.e. allergic [type I hypersensitivity] and Other systemic) and injection site reactions reported throughout the 52-week treatment period. 2. Haematological and clinical chemistry parameters. 3. Vital signs (pulse rate and systolic and diastolic blood pressure). 4. 12-lead ECG 5. Frequency of subjects with anti-mepolizumab antibody positive results.
Others	
• To evaluate the effects of mepolizumab compared with placebo on asthma control.	1. Mean change from baseline compared to placebo in Asthma Control Questionnaire (ACQ-5) score at Week 52. 2. Percent of subjects evaluated as responders as measured by ACQ-5 score at Week 52. 3. Percent of subjects evaluated as responders as measured by SGRQ score at Week 52. 4. Percent of subjects recording a favourable treatment response as measured by the Subject Rated Response to Therapy at Week 52. 5. Percent of subjects evaluated as having a favourable treatment response as measured by the Clinician Rated Response to Therapy at Week 52. 6. Mean change from baseline in daily salbutamol/albuterol use

Objectives	Endpoints
	7. Mean change from baseline in daily asthma symptom scores 8. Mean change from baseline in awakening at night due to asthma symptoms requiring rescue medication use. 9. Mean change from baseline in morning PEF 10. Mean change from baseline in clinic post-bronchodilator FEV1 at Week 52. 11. Mean number of days with oral corticosteroids taken for clinically significant exacerbations 12. Total prednisone (or equivalent) exposure for clinically significant exacerbation over the 52-week treatment period 13. Frequency of all exacerbations 14. Time to first exacerbation 15. Time to withdrawal from study treatment due to asthma exacerbations 16. Time to first exacerbation requiring hospitalization or ED visit 17. Unscheduled healthcare resource utilization (for clinically significant exacerbations and other asthma related health care) over the 52-week treatment period 18. Mean days of School/Work missed over the 52-week treatment period
Pharmacodynamics	
• To evaluate the PD of SC mepolizumab in Chinese subjects with severe asthma with eosinophilic airway inflammation.	Blood eosinophil ratio to baseline
PK Sub-Study	
• To evaluate the PK of SC mepolizumab in Chinese subjects with severe asthma with eosinophilic airway inflammation	PK parameter estimates of mepolizumab.

The primary clinical question of interest is: What is the effect of adding mepolizumab to standard of care when compared with placebo plus standard of care on the rate of exacerbations over 52 weeks in Chinese participants with severe eosinophilic asthma? This question is to be addressed in the absence of study treatment discontinuation.

The estimand is described by the following attributes:

- Population: Chinese participants with severe eosinophilic asthma.
- Treatment condition: mepolizumab 100mg SC given every 4 weeks compared to placebo every 4 weeks, both treatments given on top of standard of care. Further details on standard of care can be found in Section 6.
- Variable: number of clinically significant exacerbations over 52 weeks.
- Summary measure: annulised rate of exacerbations. Comparison between the mepolizumab arm and placebo will be assessd with the rate ratio.
- Intercurrent events:
  - Study treatment discontinuation-hypothetical strategy
- Rationale for estimand:
  Interest lies in the treatment effect when medication is taken as directed. For participants discontinuing randomised medication, use of a hypothetical strategy addresses treatment effects attributable to mepolizumab in the hypothetical scenario where participants would not discontinue from treatment.

Overall Design:

This study employs a randomized, multi-centre, placebo-controlled, double-blind, parallel-group design. A PK sub-study will be included to meet regulatory requirements.

Treatment Arms and Duration

Eligible subjects will be requested to participate for a maximum of 56 weeks (Visit 1 to the Visit 15, inclusive) in the main study. A sub-set of subjects will participate in the PK sub-study for a maximum of 64 weeks (Visit 1 to Visit 15-2, inclusive).

Following screening to assess eligibility and a run-in period for 1-4 weeks during which baseline data will be captured in an eDiary, subjects will be randomized in a 1:1 ratio to receive either mepolizumab (100 mg) SC or placebo SC added onto their existing therapy for asthma every 4 weeks for a total of 13 doses. The treatment period will conclude approximately 4 weeks after the last dose.

For subjects who enter the PK sub-study, PK samples will be collected at the time points specified in the Schedule of Activities which requires 6 additional visits (to collect PK samples only).

Number of Participants:

Approximately 429 subjects with severe asthma with eosinophilic inflammation who meet the protocol defined inclusion criteria will be screened to ensure the 1:1 (mepolizumab: placebo) randomization of 300 subjects in the study (150 subjects in the mepolizumab treatment group and 150 subjects in the placebo treatment group).

Subjects will be stratified based on blood eosinophil count at screening (≥300 cells/μL ,<300 cells/μL). A minimum of 150 subjects will be enrolled with blood eosinophil count ≥300 cells/μL.

This study will include a PK sub-study in which approximately 52 randomized subjects will provide PK samples, irrespective of the allocated treatment (to maintain the study blind). This will ensure approximately 26 subjects receiving mepolizumab will provide PK information. This is to meet the regulatory requirement of approximately 20 evaluable subjects for PK analysis.

Analysis

The study is designed to determine the effect of Mepolizumab 100mg SC on clinically significant exacerbation events, compared with placebo among Chinese subjects.

The study design mirrors the design of study MEA115588, which demonstrated benefits of mepolizumab compared to placebo for a global population of severe asthma patients with eosinophilic inflammation. This study will evaluate the effects in Chinese patients and, assuming that effects consistent with the global population are observed, a more precise evaluation of the benefit in Chinese patients will conducted by combining data from the local China study with MEA115588 using Bayesian dynamic borrowing (see Statistical Considerations in Section 9). The potential to borrow information from the global dataset is based on the premise that the underlying disease, its general management and the response to mepolizumab is similar in Chinese and non-Chinese patients.

The posterior distributions of the primary endpoint, i.e. rate ratio of events between Mepolizumab 100mg SC vs. placebo will be derived. The hypothesis of interest for treatment comparison is that the rate ratio is less than 1 (alternative hypothesis testing boundary in study MEA115588), and the study will be considered to have shown evidence that supports this hypothesis if the posterior probability that the rate ratio is less than 1 is at least 95% (a “positive result”). Rationales to support this testing criteria can be found in Section 9.4.1 (Efficacy Analyses).

The primary analyses will be performed using a generalized linear model (GLM) assuming the negative binomial distribution. The estimate of the rate ratio for mepolizumab vs. placebo as well as an estimate of the dispersion will be provided, they will be combined with global MEA115588 study using the robust mixture prior to obtain the final posterior distribution for the China rate ratio. The mean, median and 90% credible interval of this posterior distribution of the rate ratio will be reported, along with the probability that true rate ratio is less than 1.

The secondary endpoints are defined in the Objective(s)/Endpoint(s) above . No multiplicity adjustment are planned for secondary endpoints.

1.2. Schedule of Activities (SoA)

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 Table 1, are essential and required for study conduct. This section lists the procedures and parameters of each planned study assessment.

The timing of the assessments should allow the blood draw to occur at the exact nominal time. Patient Reported Outcomes questionnaires should be completed before any other assessments.

Table 1 Schedule of Activities Table

Procedures	Pre-screening	Screen/Run-in	Randomised Treatment (visit window is ± 7 days for V3-V15-2; V2-1, V2-2, V14-1, V14-2 visit window is ± 2 days from V2 or V14 in sub-study)																	Exit Visit			With-drawal
Visit	**V0[1]**	**V1**	**V2[2]**	**V 2-1[3]**	**V 2-2[3]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V 14-1[3]**	**V 14-2[3]**	**V15**	**V 15-1[3]**	**V 15-2[3]**	**VEW**
Study Week		**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**49**	**50**	**52**	**56**	**60**	
Study Day		**-28~ -7**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**343**	**350**	**364**	**392**	**420**	
Procedures																							
Written Informed Consent (main study, PK sub-study)	X[4]																						
Demography	X																						
Asthma and exacerbation history (including triggers)	X																						
Therapy history	X																						
Medical history (including cardiovascular history/risk)		X																					
Cardiovascular assessment		X																					
Concomitant Medication Assessment		X	X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
Parasitic Screening[5]		X																					
Inclusion/Exclusion Criteria		X																					
Randomisation criteria			X																				
Smoking history		X																					
Chest X-ray		X[6]																					
Efficacy Assessments																							
Exacerbation review		X	X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
Spirometry (FEV_1, FVC)		X	X			X		X			X			X			X			X			X
Reversibility Test		X	X[7]								X									X			X
ACQ-5			X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
SGRQ			X					X			X			X						X			X
Clinician rated response to therapy							X		X				X							X			X

Procedures	**Pre-screening**	**Screen/Run-in**	**Randomised Treatment (visit window is ± 7 days for V3-V15-2; V2-1, V2-2, V14-1, V14-2 visit window is ± 2 days from V2 or V14 in sub-study)**																	**Exit Visit**			**With-drawal**
Visit	**V0[1]**	**V1**	**V2[2]**	**V 2-1[3]**	**V 2-2[3]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V 14-1[3]**	**V 14-2[3]**	**V15**	**V 15-1[3]**	**V 15-2[3]**	**VEW**
Study Week		**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**49**	**50**	**52**	**56**	**60**	
Study Day		**-28~ -7**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**343**	**350**	**364**	**392**	**420**	
Subject rated response to therapy							X		X				X							X			X
Health Outcome Assessments																							
Unscheduled healthcare contact/resource utilization			X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
Safety Assessments																							
Adverse Events/Serious Adverse Event Assessment			X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
Physical Examination		X[8]	X[9]								X[9]									X[9]			X[9]
Vital Signs		X	X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
12-lead ECG		X									X									X			X
Laboratory Assessments[10]																							
Hematology with differential[11]		X	X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
Clinical Chemistry		X				X	X	X			X			X						X			
Urinalysis		X																					
Urine Pregnancy Test[12]		X	X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
FSH for suspected menopause female		X																					
Hepatitis B and C testing[13, 14]		X																					
Pharmacokinetic Sample (sub-study only)[15]			X[16]	X	X	X[16]					X[16]						X[16]	X	X	X	X	X	X
Immunogenicity sample[17]			X								X									X			X

Procedures	Pre-screening	Screen/Run-in	Randomised Treatment (visit window is ± 7 days for V3-V15-2; V2-1, V2-2, V14-1, V14-2 visit window is ± 2 days from V2 or V14 in sub-study)																	Exit Visit			With-drawal
Visit	**V0[1]**	**V1**	**V2[2]**	**V 2-1[3]**	**V 2-2[3]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V 14-1[3]**	**V 14-2[3]**	**V15**	**V 15-1[3]**	**V 15-2[3]**	**VEW**
Study Week		**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**49**	**50**	**52**	**56**	**60**	
Study Day		**-28~ -7**	**1**	**8**	**15**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**343**	**350**	**364**	**392**	**420**	
Study Supplies and Investigational Product																							
Register Visit in RAMOS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer Investigational Product			X			X	X	X	X	X	X	X	X	X	X	X	X						
Complete electronic Case Report Form (eCRF)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
eDiary dispense and training		X[18]																					
eDiary review			X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
eDiary collection																				X			X
Dispense paper worksheet		X	X			X	X	X	X	X	X	X	X	X	X	X	X						
Collect/review paper worksheet			X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
Dispense Rescue Salbutamol		X	X			X	X	X	X	X	X	X	X	X	X	X	X						
Collect Used Rescue Salbutamol			X			X	X	X	X	X	X	X	X	X	X	X	X			X			X

1. The pre-screening visit (Visit 0) can occur on the same day as the screening visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures.
2. Visit 2 can occur 1 to 4 weeks after Visit 1. Results from Visit 1 procedures must be available for review of randomization criteria.
3. Only those patients attending the PK sub-study will perform the visit. . Protocol amendment 4 updated Study Day of V2-1 (from day 7 to day 8) and V2-2 (from day 14 to day15) to clarify the duration of PK sample collection. On final PK Sample ID form and related PK CRF forms in InForm System, “VISIT 2 PREDOSE” refers to “VISIT2 DAY1”, “VISIT 2 DAY7” refers “VISIT 2 DAY8”, and “VISIT 2 DAY 14” refers to “VISIT 2 DAY15” in SoA.
4. Informed consent for the optional PK sub-study must be obtained before collecting a related sample.
5. Parasitic screening is only required in subjects who have visited high-risk countries in the past 6 months. Sites should use local laboratories.
6. Only required if results from a chest x-ray or CT-scan, taken within the past 6 months, is not available
7. Reversibility test is required at screen. If subject does not reverse ≥12% and 200 mL in FEV1 at visit 1 (screen), the procedure may be repeated at Visit 2.
8. A comprehensive physical exam should be conducted. See Section 7.3.1 for specific details of the comprehensive physical exam.
9. A brief physical exam should be conducted. See Section 7.3.1 for specific details of the brief exam.
10. During the treatment period, all lab samples (not applicable for PK samples) and procedures should be obtained pre-dose.

11. Differential results including eosinophil counts will be blinded from Visit 3 onwards.
12. Urine pregnancy testing is only required for females of child bearing potential. An assessment must be made at baseline to determine child bearing potential of each female study participant (see Table 6).
13. If hepatitis C positive confirmation by testing the same sample is required. See central laboratory manual for details.
14. For subjects who are HBsAg positive at Visit 1 or HBcAb positive (documented previous positive) reflexive testing must be conducted to assess HBV DNA.
15. Actual time for each PK sample collection needs to be recorded.
16. PK samples must be collected pre-dose.
17. For subjects who are ADA or NAB positive, PK sample collected with the immunogenicity sample (for subjects not in the PK sub-study) will be assessed.
18. Thorough eDiary training should be conducted at Visit 1 and throughout the study on an as-needed basis

2. INTRODUCTION

Mepolizumab, a humanised monoclonal antibody (IgG1, kappa, mAb), has been developed as an add-on treatment for patients with severe asthma with eosinophilic inflammation.

Mepolizumab binds with high specificity and affinity to human interleukin 5 (IL-5). By targeting IL-5, mepolizumab prevents IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits IL-5 signalling and the overexpression of peripheral blood and tissue eosinophils. Eosinophilic inflammation of the airways plays a central role in the pathogenesis of asthma.

Available data do not indicate that reduction of eosinophils has any untoward effects on normal health [Gleich, 2013]. Thus, a therapeutic strategy targeting IL-5 with mepolizumab represents a focused therapeutic option which results in reduced eosinophil levels and important clinical benefits for patients with eosinophilic inflammation associated with severe asthma who are receiving optimised standard of care therapy.

2.1. Study Rationale

Previous studies in severe asthmatic patients with eosinophilic inflammation have demonstrated a reduction in the frequency of clinically significant exacerbations [Haldar, 2009; Pavord, 2012; Ortega, 2014] and a reduction in oral corticosteroids (OCS) in OCS-dependent subjects [Nair, 2009][Bel, 2014] with mepolizumab which has also exhibited a favourable safety profile. Previous study details are described in the Investigator's Brochure [GlaxoSmithKline Document Number CM2003/00010/13] This study is a Phase III study in Chinese population, to evaluate the efficacy and safety of mepolizumab in severe asthmatics with eosinophilic inflammation. This study is similar in design to the global pivotal study MEA115588 which has established favourable benefit risk profile of mepolizumab in severe asthmatics with eosinophilic inflammation.

2.2. Background

While patients with severe asthma represent only a small percentage (5-10%) of the asthmatic population, they incur the greatest direct costs for the treatment of asthma [Ambrosino, 2012], [Bossley, 2012] . Asthma exacerbations are a major contributor to the increased healthcare costs in patients with moderate to severe asthma [Ivanova, 2012]. They are estimated to make-up between 35-50% of medical expenditures for asthma [Fuhlbrigge, 2012]. Current asthma treatment guidelines offer minimal options for the severe asthmatic patient on intensive therapy with frequent exacerbations. As a result, these patients are often exposed to repeated intermittent or long-term continuous use of systemic corticosteroids (SCS). CS provide variable efficacy benefits for patients with severe asthma, some patients are completely refractory to this treatment. Regardless of the degree of effectiveness provided by CS, all patients are at risk of the short- and long-term toxicities associated with its use. Consequently, there is a significant unmet medical need to provide better treatment options for this segment of the asthma population.
Currently available therapies are highly effective at controlling asthma symptoms and airway inflammation in the majority of patients. However, a proportion of asthma

patients remain uncontrolled despite appropriate therapy with high dose inhaled corticosteroids (ICS) or ICS with additional controller therapy (National Heart Lung and Blood Institute [NHLBI] Guidelines for the Diagnosis and Treatment of Asthma). This severe, uncontrolled population suffers from persistent symptoms and acute exacerbations of their asthma.

Severe asthma encompasses wide ranges in both clinical symptoms and in natural history. This population can be defined on the basis of medication requirements, asthma symptoms, degree of airflow limitation, and frequency of asthma exacerbations. In terms of exacerbations, two or more corticosteroid-treated exacerbations have been considered part of the typical clinical features in this patient population [Chung, 2014b].

Evidence shows that patients with severe asthma are comprised of complex, overlapping and non-overlapping phenotypes, including an eosinophilic asthma phenotype [Chung, 2014a] , which can be associated with increased asthma severity, atopy, late-onset disease, and corticosteroid insensitivity.

Previous studies have demonstrated that mepolizumab is effective and well tolerated in the eosinophilic phenotype. In Nov 2015, Mepolizumab received its first approval in the US as an add-on maintenance treatment for patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype [Nucala Label, 2015].

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of mepolizumab may be found in the Investigator's Brochure. The following section (Section 2.3.1) outlines the risk assessment and mitigation strategy for this protocol:

2.3.1. Risk Assessment

Potential Risk of Clinical significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [mepolizumab]		
Risk of Systemic (Allergic [type I hypersensitivity] and Other systemic) Reactions, including Anaphylaxis	Reactions reported to date across the mepolizumab program are summarized in the IB; see 'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'. Acute and delayed systemic reactions, including hypersensitivity reactions (e.g., anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occur within hours of administration, but in some instances had a delayed onset (i.e., days).	Daily monitoring of serious adverse events (SAEs) by medical monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team. Customized AE and SAE case report forms (CRF) are utilized for targeted collection of information on systemic reaction adverse events. Use of Joint National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 7). Subjects are to be monitored in clinic for one-hour post-injection after the first 3 administrations study treatment, and then according to standard of care for the site.
Local injection site reactions	The most common symptoms associated with subcutaneous injections included: pain, erythema, swelling, itching, and burning sensation.	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by GSK study team and/or safety review team.

Potential Risk of Clinical significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Customised AE and SAE case report form (CRF) utilised for targeted collection of information for local injection site reaction adverse events.
Risk of Immunogenicity	Mepolizumab has low immunogenic potential. Overall, the immunogenicity results from clinical studies across mepolizumab program demonstrate that the presence of ADAs is not associated with any specific adverse events, anti-mepolizumab antibodies did not discernibly impact the PK or PD of mepolizumab in the majority of subjects 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 a summary of immunogenicity findings in the 'Other Potentially Clinically Relevant Information for the Investigator' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	Blood samples are collected in clinical studies for detection of both ADA and NAB. For subjects who are ADA or NAB positive, PK samples collected with the immunogenicity samples will be assessed. Daily monitoring of serious adverse events (SAEs) by medical monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team.
Potential risk for adverse cardiovascular (CV) effects	No clinically relevant trends observed in ECG data in humans.	Daily monitoring of SAEs by medical monitor/SAE Coordinator; regular systematic

Potential Risk of Clinical significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In one earlier Phase III study in subjects with severe asthma with eosinophilic inflammation, a small numerical increase observed in serious cardiac events in the mepolizumab-treated group. However, an integrated safety analysis of phase III placebo-controlled asthma trials did not show an increased risk of cardiovascular events with mepolizumab. Cardiac events reported to date across the mepolizumab programme are summarised in the IB "Safety in Clinical studies" section under each indication studied.	review of AE/SAE data from ongoing studies by a GSK safety review team. CV monitoring per protocol. As per GSK standard practice, use of standardized CRFs to collect additional data on protocol specified CV events (e.g., myocardial infarction, hospitalization for unstable angina and congestive heart failure, arterial thrombosis, pulmonary embolism and deep vein thrombosis)
Potential risk for infections.	An integrated safety analysis of the phase III placebo-controlled asthma trials showed similar reports of infections, including serious and opportunistic, across treatment groups. Infections reported to date across the mepolizumab development program are summarized in the IB; see 'Special Precautions and Warnings' (for exclusion of subjects with underlying parasitic infections) and 'Undesirable Effects' sections located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	Daily monitoring of SAEs by medical monitor/ SAE Coordinator; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team Subjects with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are excluded
Potential risk for malignancies -	An integrated safety analysis of phase III placebo-controlled asthma trials showed similar	Daily monitoring of SAEs by medical monitor/ SAE Coordinator; regular systematic review of

Potential Risk of Clinical significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	reports of malignancies across treatment groups. Malignancies reported to date across the mepolizumab development program are summarized in the IB section "Safety in Clinical Studies" under each indication.	AE/SAE data from ongoing studies by a GSK safety review team
Study Procedures		
Potential risk for injury with phlebotomy	Risks with phlebotomy include bruising, bleeding, infection, nerve damage.	Procedures to be performed by trained personnel (i.e., study nurse)
Inclusion of a placebo arm	The objective of the study is to compare the efficacy and safety of mepolizumab versus placebo in asthmatics subjects receiving standard-of-care therapy.	Because all subjects are receiving background standard-of-care therapy in this study the Sponsor considers inclusion of a placebo arm to be justified.
Blinding eosinophil counts	This study is a double-blind study which will be used to support approval for the use of mepolizumab in the reduction of clinical significant exacerbations in patients with severe asthma with eosinophilic inflammation. Unblinding eosinophil counts may compromise the integrity of the study.	Patients will be seen monthly by qualified investigators. Neither the site nor GSK personnel will be sent results from the central laboratory for: i) absolute eosinophil count or ii) white blood count differentials (% neutrophil, lymphocyte, monocyte, eosinophil and basophil), for each subject's duration in the study for any visits post-randomization. However, sites will be sent total white blood counts throughout the study.

2.3.2. Benefit Assessment

Exacerbations are a major concern to asthma patients and lead to a worsening of the quality of life for subjects. Mepolizumab has demonstrated significant clinical benefit in reducing exacerbations in severe asthma where eosinophilia is considered to play a key role in the pathology.

In this study, benefit considerations for a subject may include:

- Potential to receive active drug during study conduct that may have clinical utility. Interventions in at risk populations that can reduce or eliminate serious exacerbations will improve a patient's quality of life and may reduce hospitalizations.

- Contributing to the process of developing new therapies in an area of unmet need.

- Data obtained from study 201536 will provide a robust evaluation of the efficacy and safety of mepolizumab in the Chinese population. Subjects participating in this study will be required to attend visits approximately every 4 weeks and therefore may benefit from the additional monitoring to their current standard asthma care.

- Medical evaluations/assessments associated with study procedures.

2.3.3. Overall Benefit: Risk Conclusion

Mepolizumab is approved for the treatment of severe eosinophilic asthma at a dose of 100 mg SC every four weeks in the US, all EU Member States, Japan, as well as over 10 further countries.

Mepolizumab has a well-characterised efficacy and safety profile supported by the clinical development programme in the treatment of severe eosinophilic asthma. Data from the clinical development programme show that mepolizumab is effective in reducing the rate of clinically significant exacerbations, improving asthma control and quality of life, and reducing the requirement for daily systemic corticosteroids (SCS) in patients with severe eosinophilic asthma. Overall, the safety profile showed mepolizumab to be well-tolerated, and comparable to placebo. Acute and delayed systemic reactions, including hypersensitivity reactions (e.g., anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. In this study, systemic reaction events will be collected utilizing targeted case report forms, and subjects will be monitored for at least an hour following first 3 administrations of study intervention, and then per institutional guidelines.

The benefit risk profile of mepolizumab for the treatment of severe eosinophilic asthma is positive.

3. OBJECTIVES AND ENDPOINTS

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To evaluate the efficacy of mepolizumab 100 mg subcutaneous (SC) every 4 weeks versus placebo on the frequency of clinically significant exacerbations in adult and adolescent Chinese subjects with severe asthma with eosinophilic airway inflammation.	Frequency of clinically significant exacerbations of asthma over the 52-week treatment period. Clinically significant exacerbations are defined as: Worsening of asthma which requires use of systemic corticosteroids (SCS)[1] and/or hospitalizations and/or Emergency Department (ED) visits. *[1]For all subjects, i.v. or oral corticosteroid for at least 3 days or a single IM CS dose is required. For subjects on maintenance systemic corticosteroids (SCS), at least double the existing maintenance dose for at least 3 days is required.*
Secondary Efficacy	
• To evaluate the effects of mepolizumab compared with placebo on a range of clinical markers of asthma control, including exacerbations, lung function, and quality of life.	1. Time to first clinically significant exacerbations 2. Mean change in St. George's Respiratory Questionnaire (SGRQ) at Week 52 3. Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits over the 52-week treatment period 4. Frequency of exacerbations requiring hospitalisation over the 52-week treatment period 5. Mean change from baseline in clinic pre-bronchodilator FEV_1 at Week 52
Safety	
• To evaluate the safety and tolerability of mepolizumab compared with placebo, in subjects with severe asthma with eosinophilic inflammation.	1. Adverse Event including systemic (i.e. allergic [type I hypersensitivity] and other systemic) and injection site reactions reported throughout the 52-week treatment period. 2. Haematological and clinical chemistry parameters. 3. Vital signs (pulse rate and systolic and diastolic blood pressure). 4. 12-lead ECG

Objectives	Endpoints
	5. Frequency of subjects with anti-mepolizumab antibody positive results.
Others	
• To evaluate the effects of mepolizumab compared with placebo on asthma control.	1. Mean change from baseline compared to placebo in Asthma Control Questionnaire (ACQ-5) score at Week 52. 2. Percent of subjects evaluated as responders as measured by ACQ-5 score at Week 52. 3. Percent of subjects evaluated as responders as measured by SGRQ score at Week 52. 4. Percent of subjects recording a favourable treatment response as measured by the Subject Rated Response to Therapy at Week 52. 5. Percent of subjects evaluated as having a favourable treatment response as measured by the Clinician Rated Response to Therapy at Week 52. 6. Mean change from baseline in daily salbutamol/albuterol use 7. Mean change from baseline in daily asthma symptom scores 8. Mean change from baseline in awakening at night due to asthma symptoms requiring rescue medication use. 9. Mean change from baseline in morning PEF 10. Mean change from baseline in clinic post-bronchodilator FEV1 at Week 52. 11. Mean number of days with oral corticosteroids taken for clinically significant exacerbations 12. Total prednisone (or equivalent) exposure for clinically significant exacerbations over the 52-week treatment period 13. Frequency of all exacerbations 14. Time to first exacerbation 15. Time to withdrawal from study treatment due to asthma exacerbations 16. Time to first exacerbation requiring hospitalization or ED visit

Objectives	Endpoints
	17. Unscheduled healthcare resource utilization (for clinically significant exacerbations and other asthma related health care) over the 52-week treatment period 18. Mean days of School/Work missed over the 52-week treatment period
Pharmacodynamics	
• To evaluate the PD of SC mepolizumab in Chinese subjects with severe asthma with eosinophilic inflammation.	Blood eosinophil ratio to baseline

3.1. Pharmacokinetic Sub-Study

The endpoints outlined in Table 3 are only applicable to the pharmacokinetic (PK) sub-study (see Section 9.4.3 or further details).

Table 3 Pharmacokinetic Sub-Study Objectives and Endpoints

Objective	Endpoints
• To evaluate the PK of SC mepolizumab in Chinese subjects with severe asthma with eosinophilic inflammation.	PK parameter estimates of mepolizumab

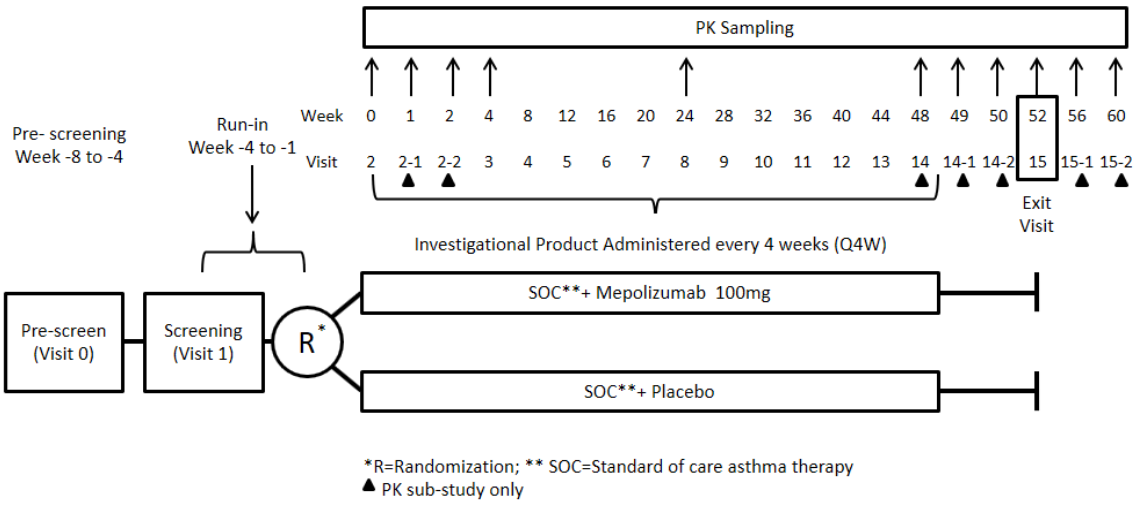
4. STUDY DESIGN

4.1. Overall Design

This study employs a multi-centre, randomized, placebo-controlled, double-blind, parallel-group design (Figure 1). In the main study, there will be a total of 16 clinic visits conducted on an outpatient basis. A pre-screening visit (V0) will be conducted to sign the informed consent form (ICF) and review demography, asthma history and concomitant medications. Once the ICF is signed the subject will be assigned a subject identifier. Subjects who meet the eligibility criteria at Screening (Visit 1) will complete a 1 to 4 weeks run-in period followed by a double-blind 52-week treatment period. The run-in period is designed to capture baseline eDiary data. Subjects who experience an asthma exacerbation during the run-in should receive treatment for their exacerbation and remain in the run-in period until the subject has returned to their baseline asthma status for at least one week. Those subjects that are not able/eligible to be randomized at the end of the 4-week run-in period will be deemed run-in failures. Clinic visits will be at Pre-screening (Visit 0), Screening, Randomization (Day 1, Week 0), then every 4 weeks during treatment period until the Exit Visit at Week 52. The Exit Visit (Visit 15) represents the last day of study (i.e. 4 weeks after the last dose given at Visit 14). If a subject withdraws from this study, an early withdrawal visit (Visit Early Withdrawal [VEW]) will be performed within 4 weeks after the last dose (Section 5.5). The total duration of subject participation in the main study, including run-in will be 53 to 56 weeks. Subjects will remain on their current maintenance therapy throughout the run-in and double-blind treatment administration periods.

Evaluation of mepolizumab PK will be conducted in a sub-set of subjects (Section 7.5). At Visit 2, about 52 subjects who are randomized will be entered into the PK sub-study if consents for sub-study are obtained. With a ratio of 1:1 (mepolizumab: placebo), approximately 26 subjects are therefore expected to be allocated to the mepolizumab treatment group. This is to meet the regulatory requirement of approximately 20 evaluable subjects for PK analysis. Blood samples for pharmacokinetics will be collected at the time points specified in the Schedule of Activities (Section 1.2). For subjects who enter the PK sub-study, a total of 11 visits will be performed to collect PK sampling, of which 6 additional visits compare with main study at Week 1, 2 and Week 49, 50, 56, 60 (i.e. 1, 2, 8, 12 weeks after last dose) will be conducted. Therefore, the total duration of subject participation, including run-in, will be 61 to 64 weeks.

Figure 1 Study Schematic



4.2. Treatment Arms and Duration

Eligible subjects will be requested to participate for a maximum of 56 weeks (Visit 1 to Visit 15, inclusive) in the main study. A sub-set of subjects will participate in the PK sub-study for a total of 64 weeks (Visit 1 to Visit 15-2, inclusive). Subjects will remain on their existing standard of care asthma therapy whilst completing the three phases of the study, as described in Table 4.

Subjects who meet the eligibility criteria will be randomized to receive either mepolizumab (100 mg) or placebo at a 1:1 ratio.

Subjects will be stratified based on blood eosinophil count at screening (≥300 cells/μL, <300 cells/μL). A minimum of 150 subjects will be enrolled with blood eosinophil count ≥300 cells/μL.

Table 4 Study Phases

Phase	Phase Title	Duration	Description
1	Pre-screening	0-4 weeks	Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures.
2	Screening / Run-in	1 to 4 weeks	Subjects who meet all the eligibility criteria at Visit 1 (Screening), will enter the run-in period

Phase	Phase Title	Duration	Description
			for a minimum of 1 week and a maximum of 4 weeks in order to continue to assess the subject's eligibility for the study as well as to collect baseline eDiary data. Those subjects that are not eligible to continue in the study at the end of the 4-week run-in period will be deemed run-in failures (see Section 5.4).
3	Treatment	52 weeks	At Visit 2 (Week 0) those subjects who successfully complete the run-in period as well as meet the pre-defined randomization criteria will be randomized; those subjects that do not meet the pre-defined randomization criteria will be deemed run-in failures (see Section 5.4). Study medication will be administered SC every 4 weeks for a total of 13 doses (Visit 2 to Visit 14, inclusive). The treatment period will conclude approximately 4 weeks after the subject was administered their last dose of double-blind study treatment. PK samples will be collected at Week 0, 1, 2, 4, 24, and Week 48, 49, 50, 52, 56, 60 (or 0, 1, 2, 4, 8, 12 weeks after last dose) in subjects who provided consents for PK sub-study.

*For information on criteria relating to study treatment withdrawal, refer to Section 5.5

4.3. Type and Number of Subjects

Approximately 429 subjects will be screened to achieve 300 randomized at a ratio of 1:1 (150 subjects in mepolizumab arm and 150 subjects in placebo arm).

This study will include a PK sub-study in which approximately 52 randomized subjects will provide PK samples, irrespective of the allocated treatment (to maintain the study blind). This will ensure approximately 26 subjects receiving mepolizumab will provide PK information. This is to meet the regulatory requirement of approximately 20 evaluable subjects for PK analysis.

4.4. Scientific Rationale for Study Design

This study is similar in design to the Phase III global pivotal study MEA115588, and will be conducted in a similar patient population, using the same definition of the primary endpoint. The target population will be severe asthmatics with eosinophilic phenotype who exacerbate despite regular use of optimized therapy in the 12 months prior to study start (per inclusion criteria). Results of study MEA115588 have shown statistically and clinically significant improvements in reducing the frequency of protocol defined exacerbations in this population treated with mepolizumab. The current study will use the same peripheral blood eosinophil counts to identify eosinophilic subjects (i.e. either a peripheral blood eosinophil count of ≥300 cells/μL related to asthma during the past 12 months prior the study, or a peripheral blood eosinophil count of ≥150 cells/μL at Visit 1 that was related to asthma) in combination with criteria similar to those of the ATS workshop on severe refractory asthma [ATS workshop, 2000] at study start.

In study MEA115588, optimized therapy included a history of regular use of high-dose ICS for 12 months prior to screening, which refers to a FP dose equivalent or above 1000 mcg/day (via a dry powder inhaler) for a monotherapy or the highest approved maintenance dose in the local country for an ICS/LABA combination. The medium dose ICS/LABAs (Salmeterol/FP 50/250 mcg bid equivalent or above) is considered appropriate and as the optimized therapy in this protocol since it is more commonly used than the highest approved ICS/LABAs (Salmeterol/FP 50/500 mcg bid) in China as the maintenance therapy in severe asthmatics. (Section 5.1). In the current study, we adopted a 52-week treatment period because it is reasonable for collecting exacerbations as well as safety data.

All subjects will continue on their baseline optimized asthma medications throughout the entire treatment duration. If for a medical reason the subject must change their baseline asthma medication the primary investigator should, wherever possible, discuss this with the study Medical Monitor prior to implementation. Allowing use of optimized therapy supports inclusion of a placebo group contributing to a favourable benefit: risk profile for participating subjects.

The 1 to 4-week run-in period allows for the assessment of subject understanding of and compliance with the daily eDiary, to establish baseline diary symptoms, and to allow adequate time for receipt of results from assessments collected at Visit 1.

4.5. Justification for Dose

GSK is proposing this local Phase III study to be conducted in China in patients with severe asthma with eosinophilic inflammation. The proposed dose and dosing regimen in Chinese patients is 100 mg administered subcutaneously (SC) every 4 week, the same as the global therapeutic dose regimen. Mepolizumab 100 mg SC (as well as the IV equivalent dose 75 mg) administered once every 4 weeks, have been studied extensively in the global Phase III studies (MEA112997, pivotal study MEA115588, and MEA115575).

Mepolizumab pharmacokinetic information at the proposed clinical dose once every 4 weeks is available in East Asian subjects (recruited in Japan and Korea) with severe asthma with eosinophilic inflammation from study MEA115588. Additional pharmacokinetic data are available following IV administration of doses from 75 mg up to 750 mg in East Asian subjects (recruited in Korea) with severe asthma with eosinophilic inflammation from study MEA112997. The population pharmacokinetic analysis of IV and SC mepolizumab data did not identify Race, including East Asian ancestry, as a covariate of mepolizumab exposure in subjects with severe asthma with eosinophilic inflammation. The average mepolizumab exposure (Cmax and AUC) in East Asian subjects with severe asthma with eosinophilic inflammation in the Japanese +Korean cohort is generally similar to that of the overall population and the cohort of White/Caucasian subjects (MEA115588).

Over 3344 subjects have received treatment with mepolizumab in studies completed by Sep 2015. All trials have shown that mepolizumab is well tolerated when administered by IV, IM, or SC routes.

The safety profile (study MEA115588) in severe asthma subjects from Japan and Korea is generally consistent with the overall population of relevant studies (MEA112997, pivotal study MEA115588, and MEA115575). Study MEA112997 examined intravenously administered mepolizumab doses of 75, 250 and 750 mg, which provided additional East Asian safety data over the 10-fold dose range in 24 subjects studied in Korea. The safety profile showed no differentiation across this 10-fold dose range. Based on the safety data available there was no signal of an inter-ethnic difference of concern for mepolizumab 100 mg SC administered once every 4 weeks for 52 weeks in subjects to be recruited in China in the present study.

In the East Asian subjects as well as the overall population of the mepolizumab severe asthma development programme, anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics, pharmacodynamics, or safety of mepolizumab. To date, there is no evidence to suggest that the immunogenicity profile of mepolizumab differs in East Asian subjects, relative to other subjects in the overall mepolizumab clinical programme.

In conclusion, based on the information discussed above, we believe that mepolizumab 100 mg SC once every 4 weeks is an appropriate dose to study in Chinese subjects with severe asthma with eosinophilic inflammation.

5. STUDY POPULATION

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB GlaxoSmithKline Document Number CM2003/00010/13 .

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

5.1. Inclusion Criteria

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

1. **Informed Consent:** Able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. Subjects must be able to read, comprehend, and write at a level sufficient to complete study related materials.
2. **Age and Weight:** At least 12 years of age at Visit 0 and a minimum weight of 40 kg.
3. **FEV1**: Persistent airflow obstruction as indicated by:
    - For subjects ≥18 years of age at visit 1, a pre-bronchodilator FEV_1 <80% predicted normal values calculated by Quanjer reference equations [Quanjer, 2012]
    - For subjects 12-17 years of age at visit 1:

      • A pre-bronchodilator FEV1 <90% predicted (Quanjer, 2012) recorded at Visit 1 OR

      • FEV_1: FVC ratio <0.8 recorded at visit 1
4. **Eosinophilic information**: Prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma as per Randomization Criteria 1.
5. **Inhaled Corticosteroid:** Regular treatment with high dose inhaled corticosteroid (ICS) in the 12 months prior to Visit 1, of which at least 9 months accumulated documented is required, the 3 months prior to Visit 1 is mandatory. With or without maintenance oral corticosteroids(OCS)*.

   ICS dose must be ≥500 mcg/day fluticasone propionate (FP) or equivalent daily (for ICS/LABA combination preparations, Seretide 50/250 mcg bid and above or equivalent will meet this ICS criteria). *[Maintenance OCS is defined as a prescribed regimen of a minimum average daily dose of prednisone 5mg (or equivalent)].
6. **Controller Medication:** Current treatment with one or more additional controller medication, besides ICS. At least one additional controller medication must have

been regularly used for at least 3 months prior to Visit 1. [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline]

7. **Exacerbation history:** Previously confirmed history of two or more exacerbations requiring treatment with systemic CS (intramuscular (IM), intravenous, or oral), in the 12 months prior to Visit 1, despite the use of high-dose ICS. For subjects receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold increase or greater in the dose for at least 3 days is required.
8. **Gender:** Male or Female

   Female participants:

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

   - Is not a woman of childbearing potential (WOCBP)

     OR

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

   A WOCBP must have a negative highly sensitive pregnancy (Appendix 4) test before the first dose of study intervention.

   If 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. FSH will be assessed to confirm child-bearing status as needed in non WOCBP.

5.2. Exclusion Criteria

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

1. **Smoking history:** Current smokers or former smokers with a smoking history of ≥10 pack years (number of pack years = (number of cigarettes per day /20) x number of years smoked). A former smoker is defined as a subject who quit smoking at least 6 months prior to Visit 1.
2. **Concurrent Respiratory Disease:** Presence of a known pre-existing, clinically significant* lung condition other than asthma, in the opinion of the Investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study. This includes current bacterial or viral infection of the upper or lower respiratory tract, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer.

*Clinically Significant is defined as any disease/condition that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

3. **Abnormal Chest X-ray (or CT scan):** A chest X-ray (or CT scan) that reveals evidence of clinically significant abnormalities not believed to be due to the presence of asthma. If a chest X-ray (or CT scan) is not available within 6 months prior to Visit 1, then a chest X-ray must be conducted.
4. **Bronchial Thermoplasty and Radiotherapy**: Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to visit 1 and throughout the study.
5. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (Subjects that had localized carcinoma of the skin which was resected for cure will not be excluded).
6. **Liver Disease:** Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice or cirrhosis.

   NOTES:
   Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C -eg, presence of hepatitis B surface antigen [HBsAg] or positive hepatitis C antibody test result) is acceptable if the participant otherwise meets entry criteria

   ALT >2 xULN

   Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
7. **Cardiovascular:** Subjects who have known, pre-existing severe or clinically significant cardiovascular disease uncontrolled with standard treatment. Including but not limited to:
   1) known ejection fraction of <30% **OR**
   2) severe heart failure meeting New York Heart Association Class IV (see Appendix 8) classification **OR**
   3) hospitalised in the 12 months prior to Visit 1 for severe heart failure meeting New York Heart Association Class III (see Appendix 8) **OR**
   4) angina diagnosed less than 3 months prior to Visit 1 or at Visit 1
8. **ECG Assessment**: QTc(F) >450msec or QTc(F) >480 msec for subjects with Bundle Branch Block at Visit 1 is exclusive.
9. **Other Concurrent Medical Conditions:** Subjects who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.

   Current malignancy except for basal and squamous skin cancer.

10. **Eosinophilic Diseases:** Subjects with other conditions that could lead to elevated eosinophils such as Hypereosiniophilic Syndromes, including Churg-Strauss Syndrome, or Eosinophilic Esophaghitis.
11. **Parasitic infection:** Subjects with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are also excluded.
12. **Alcohol/Substance Abuse:** A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1.

    Alcohol abuse is defined as: an average weekly intake of greater than 21 units or an average daily intake of greater than three units (males) or defined as an average weekly intake of greater than 14 units or an average daily intake of greater than two units (females).

    One unit was equivalent to a half-pint (220 mL) of beer or one (25 mL) measure of spirits or one glass (125 mL) of wine.
13. **Immunodeficiency:** A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of corticosteroids taken as therapy for asthma.
14. **Xolair:** Subjects who have received omalizumab [Xolair] within 130 days of Visit 1.
15. **Other Monoclonal Antibodies:** Subjects who have received any monoclonal antibodies (other than Xolair) to treat inflammatory disease within 5 half-lives of visit 1.
16. **Herbals:** Use of herbals within 7 days prior to visit 1, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.
17. **Investigational Medications:** Subjects who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to visit 1 (this also includes investigational formulations of marketed products).
18. **Hypersensitivity:** Subjects with allergy/intolerance to a monoclonal antibody or biologic.
19. **Pregnancy:** Subjects who are pregnant or breastfeeding. Patients should not be enrolled if they plan to become pregnant during the time of study participation.
20. **Adherence:** Subjects who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.
21. **Previous participation:** Previously participated in any study with mepolizumab and received investigational product (including placebo).
22. **Affiliation with Investigator Site**: A subject will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.
23. **Questionable validity of consent**: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.

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

5.3. Randomization Criteria

Those subjects who meet the randomization criteria will be randomized into the study.

At the end of the run-in period, study subjects must fulfil the following additional criteria in order to be randomized to study treatment:

1. **Eosinophilic criteria:**
    1) Documented peripheral blood eosinophil count of ≥300cells/μL that is related to asthma in the past 12 months prior to Visit 1

    OR

    2) A peripheral blood eosinophil count of ≥150cells/μL at Visit 1 that is related to asthma.
2. **Asthma:** Evidence of asthma as documented by either:
    1) Airway reversibility (FEV_1≥12% and 200 mL) demonstrated at Visit 1 or Visit 2 OR
    2) Airway reversibility (FEV_1≥12% and 200 mL) documented in the 12 months prior to visit 2 (randomization visit) **OR**
    3) Airway hyperresponsiveness (PC_{20} of <8mg/mL or PD_{20} of <7.8 μmol methacholine/histamine) documented in the 12 months prior to visit 2 (randomization visit) **OR**
    4) Airflow variability in clinic FEV_1 ≥20% between two clinic visits documented in the 12 months prior to visit 2 (randomization visit) (FEV_1 recorded during an exacerbation will not be valid) **OR**
    5) Airflow variability as indicated by >20% diurnal variability in peak flow observed on 3 or more days during the run-in
3. **eDiary Compliance:** Compliance with completion of the eDiary defined as:
    1) Completion of symptom scores on 4 or more days out of the last 7 days immediately preceding Visit 2.
    2) Completion of information relating to rescue medication use on 4 or more days out of the last 7 days immediately preceding Visit 2.
    3) Completion of PEF measurements on 4 or more days out of the last 7 days immediately preceding Visit 2.
4. **Hepatitis B:** Subjects who are Hepatitis B surface antigen (HBsAg) positive or HBcAb positive must not have a HBV DNA level ≥2000 IU/mL at Visit 1.
5. **Abnormal clinically significant finding**: Subjects have no evidence of clinically significant findings in their laboratory screening tests including liver chemistry at Visit 1.

6. **Asthma Exacerbation:** Subjects with an ongoing asthma exacerbation should have their randomization visit delayed until the investigator considers the subject has returned to their baseline asthma status at least 1 week prior to Visit 2. If the 4-week screening period has elapsed then the subject should be considered a run-in failure.

   An exacerbation is defined as worsening of asthma requiring the use of systemic corticosteroids (SCS) and/or emergency department visit, or hospitalisation.

7. **Maintenance Asthma Therapy:** No changes in the dose or regimen of baseline ICS and/or additional controller medication (except for treatment of an exacerbation) during the run-in period. Herbals should not be used during the run-in period, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

5.4. Pre-Screening/ Screening/Baseline/Run-in Failures

A subject will be assigned a subject number at the time the informed consent is signed. A subject who is assigned a subject number but does not have a Visit 1 procedure will be considered a pre-screen failure.

For the purposes of this study, screening failures and run-in failures will be defined as follows:

> **Screening failures:** those subjects that complete at least one Visit 1 (Screening) procedure but do not enter the run-in period.
>
> **Run-in failures:** those subjects that enter the run-in period but are not subsequently randomized.

RAMOS-NG will be contacted to report screening and run-in failures.

In order to ensure transparent reporting of screen/run-in failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen/run-in failure information is required including demography, screen/run-in failure details, eligibility criteria, and any Serious Adverse Events (further details are provided in the study-specific eCRF completion guidelines document).

5.5. Withdrawal/Stopping Criteria

Withdrawal from study treatment

Subjects may be withdrawn from study treatment at anytime by the Investigator if it is considered to be detrimental for them to continue in study treatment.

A subject must be withdrawn from study treatment if any of the following stopping criteria are met:

- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria (Section 5.5.1)
- QT: Meets any of the protocol-defined stopping criteria (Section 5.5.2)
- Pregnancy: Positive pregnancy test

Other reasons for withdrawal can include: an adverse event (including abnormal liver function test other than stopping criteria or abnormal laboratory results), Investigator unblinded study treatment, clinically significant abnormality identified on ECG reading other than stopping criteria, lost to follow-up, protocol violation, lack of efficacy, sponsor terminated study, non-compliance, or for any other reason.

Subjects who withdraw from study treatment prematurely (for any reason) should, where possible, continue to be followed-up as per protocol until the completion of the Exist Visit assessments. If this is not possible, the Investigator must encourage the subject to participate in as much of the study (scheduled visits and activities, record eDiary data) as they are willing (or able) to. If subject cannot attend the visit on site, telephone contact is acceptable to collect below information: asthma exacerbation, AE/SAE, concomitant medication and to encourage subjects continue to record eDiary data.

Withdrawal from the study

Subjects are also free to withdraw consent to participate in the study at anytime. Every effort should be made to have them return to the clinic for an Early Withdrawal Visit and to return all study related materials. In those instances where the subject specifies the reason for withdrawal of consent, this information will be captured in the eCRF. Patients will not be followed for any reason after consent has been withdrawn.

A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

In the event a subject withdraws from study at, or during, a scheduled visit, and does not receive investigational product, an Early Withdrawal Visit is not required. However, all study procedures scheduled at an Early Withdrawal Visit must be performed at this visit instead.

The primary reason for withdrawal from study will be recorded in the eCRF and any data collected up until the point of withdrawal from study will be used in the analyses when appropriate.

Pharmacokinetic Sub-Study Withdrawal

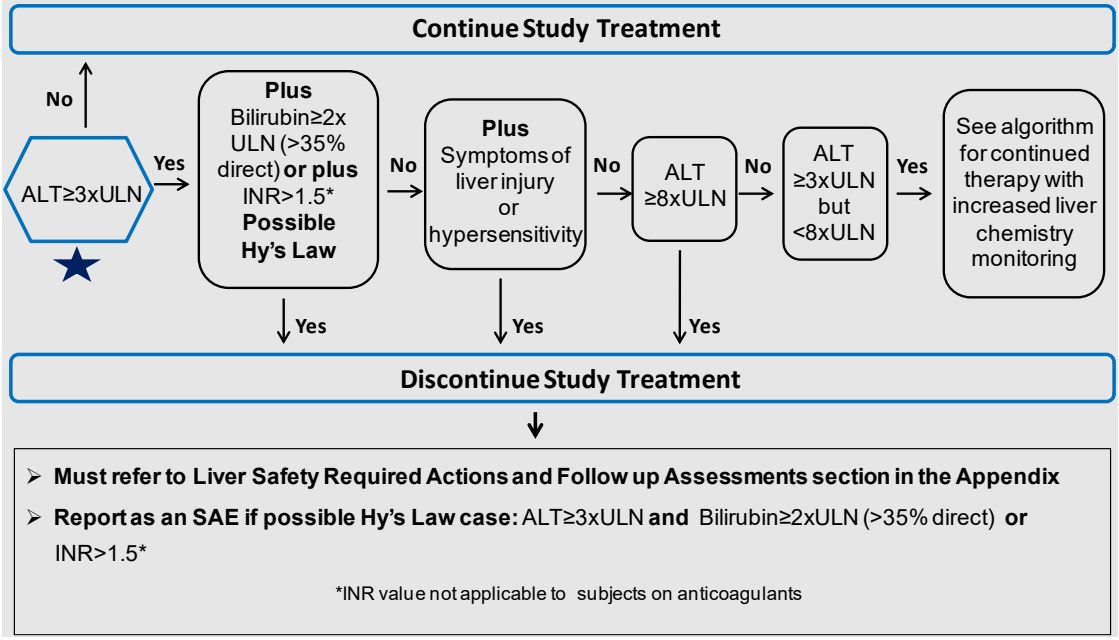
A subject may withdraw from the PK sub-study at any time at his/her own request; a subject may also be withdrawn from the sub-study at any time at the discretion of the investigator.

Subjects who withdraw early from the main study must also withdraw from the sub-study; however, subjects who withdraw early from the sub-study do not automatically have to withdraw from the main study.

Details of withdrawal procedures are provided in the SRM.

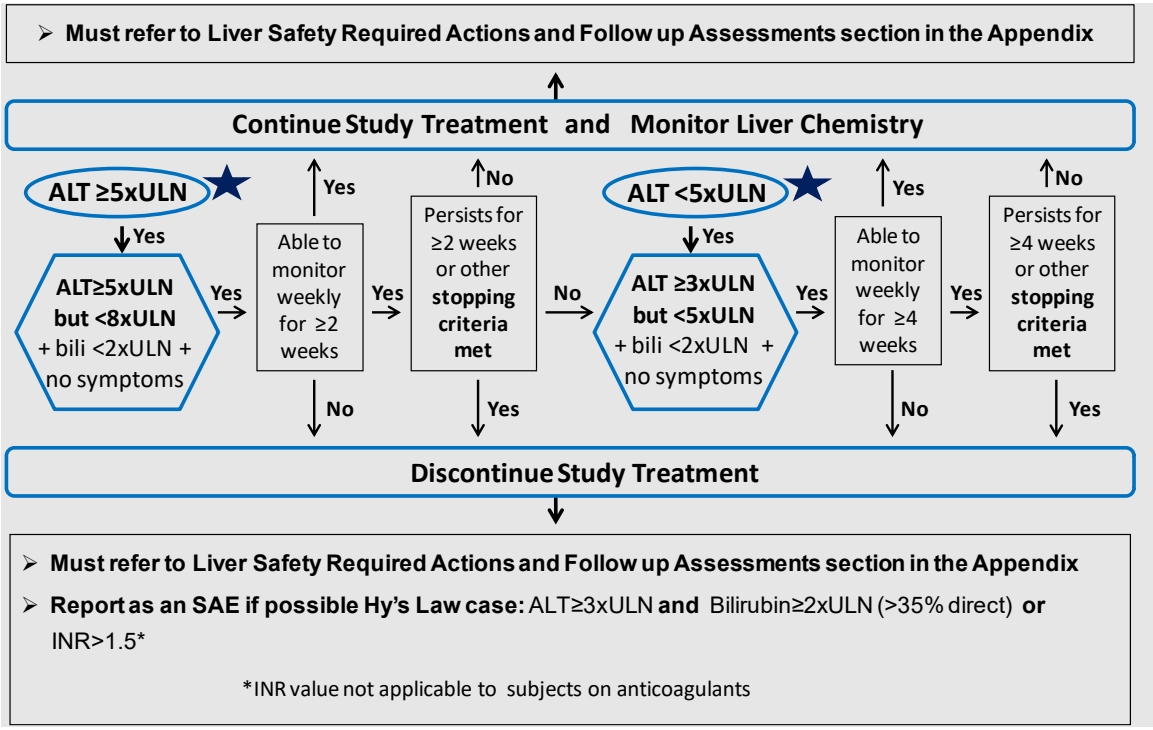
5.5.1. Liver Chemistry Stopping Criteria

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



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

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



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

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.5.1.1. Study Treatment Restart or Rechallenge

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

5.5.2. QTc Stopping Criteria

A participant who meets the bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study intervention:

For this study, the following QTc stopping criteria will apply:

- QTcF>500 msec or uncorrected QT>600 msec
- Change from baseline: QTcF> 60msec
- For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

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

5.6. Subject and Study Completion

Subjects will be regarded as having completed the study if they complete all phases of the study (run-in, double-blind treatment administration, and Exit Visit) OR although they prematurely discontinue study treatment but still complete the Week 52 Visit.

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

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Mepolizumab is a humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. Mepolizumab will be provided as a lyophilised cake in sterile vials for individual use. The vial will be reconstituted with Sterile Water for Injection, just prior to use. The placebo in this study will be 0.9% sodium chloride solution and will be provided byGSK. Further information on the preparation and administration of study treatment can be found in Section 6.5.

Trade label salbutamol metered dose inhalers (MDIs) will be provided. Subjects will be dispensed an MDI at the time of Pre-Screening to be used to primarily treat asthma symptoms on an as needed basis but also during the reversibility assessments (see Section 7.2.4). The MDI should be replaced as needed and retained at the Exit Visit (or Early Withdrawal Visit, as applicable).

6.2. Study Treatment Assignment

At Visit 2 (Week 0) those subjects who meet the randomization eligibility criteria will be randomized in a 1:1 ratio (mepolizumab: placebo) to receive one of the following study treatments in addition to their baseline asthma treatment:

Mepolizumab 100 mg SC into the upper arm or thigh

Placebo 0.9% sodium chloride SC into the upper arm or thigh

Subjects will be stratified based on blood eosinophil count at screening (≥300 cells/μL , <300 cells/μL). A minimum of 150 subjects will be enrolled with blood eosinophil count ≥300 cells/μL.

Subjects eligible to enter the study will be assigned to treatment randomly via IWRS. In addition, IWRS will also be used to manage the entry of eligible subjects into the pharmacokinetic sub-study; subjects may not be permitted to enter the pharmacokinetic sub-study if the planned number of subjects in mepolizumab treatment arm has been reached.

6.3. Blinding

Mepolizumab and placebo will be prepared by a designated **unblinded** member of the study site staff (i.e. a qualified person who is independent of the protocol-defined study assessments) and will be administered by a designated **blinded** member of the site staff. Once prepared, mepolizumab and placebo will be identical in appearance. The blinding of all those involved in the evaluation of the study treatment (e.g. physician/nurse as well

as the subject) shall be maintained at all times, therefore, procedures must be in-place at the study site to ensure that this blinding is maintained.

With regards to the emergency unblinding of the study treatment assigned to a specific subject, the following will apply:

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

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject 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 subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of placebo or reconstitution of mepolizumab will be detailed in the unblinded staff manual.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment.

A qualified **unblinded** site staff member assigned to the study will be required to prepare the appropriate study treatment according to the study subject's treatment assignment (see Section 6.2 for further details on treatment assignment):

- **Mepolizumab:** 1 mL of reconstituted mepolizumab (equivalent to 100 mg of mepolizumab) will be drawn into a 1 mL polypropylene syringe.
- **Placebo:** 1 mL of 0.9% sodium chloride solution will be drawn into a 1 mL polypropylene syringe.

A **blinded** staff member will administer the study treatment into the subject's upper arm or thigh via SC injection. Subjects will be monitored for 1 hour after the first three administrations of study treatment and then according to monitoring policies for the center. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the patient including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.

All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator's unblended site staff. In accordance with local regulatory requirements, the investigator's designated unblinded site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and the investigator or designated blinded site staff will document the amount administered to study subjects. The designated unblinded site staff will document the amount returned by blinded staff, and the amount received from and returned to GSK, when applicable. Product dispensing/accountability logs will be maintained by a designated unblinded member of the site staff throughout the study. Further guidance and information for final disposition of unused study treatment are provided in the SRM.

Under normal conditions of handling and administration, study treatment is not expected to pose 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.

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

6.6. Study Treatment Compliance

Mepolizumab and placebo will be administered via SC injection to subjects at the study site. Administration will be documented in the source documents and reported in the eCRF.

6.7. Treatment of Study Treatment Overdose

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

6.8. Treatment after the End of the Study

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

6.9. Concomitant Therapy

6.9.1. Permitted Medications and Non-Drug Therapies

All concomitant medications taken during the study will be recorded in the eCRF as well as the ICS usage in the past 12 months prior to Visit 1 and other additional controllers in the past 3 months prior to Visit 1. The minimum requirement is that drug name and the dates of administration are to be recorded. However, for ICS and OCS, the dose must be recorded as well as any dose changes.

All additional asthma medications such as LABA, theophyllines or anti-leukotrienes will be continually used with the same dose and regimen if they have been taken regularly in the 3 months prior to randomization (Visit 2, Week 0). Maintenance OCS will be permitted. SABAs and SAMAs are permitted as long as they are withheld for at least 6 hours prior to clinic visit.

If for any reasons (except asthma exacerbation) the participant must change their maintenance asthma treatment medications, the investigator must discuss the change with the Medical Monitor prior. Any changes of maintenance asthma treatment should be recorded in the eCRF.

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

6.9.2. Prohibited Medications and Non-Drug Therapies

The following medications are not allowed prior to screening according to the following schedule or during the study:

Table 5 Medications not allowed prior to the screening visit and throughout the study

Medication	**Washout Time Prior to Screening Visit**
Herbals*	7 days
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab [Xolair]	130 days
Other biological	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months
Immunosuppressive medications such as those listed below (not all inclusive)	
• Methotrexate, troleandomycin, cyclosporin, azathioprine	1 month
• Corticosteroids intramuscular, long-acting depot if used to treat a condition other than asthma	3 months
• Regular systemic (oral or parenteral) corticosteroids for the treatment of conditions other than asthma	3 months
• Oral gold	3 months
• Chemotherapy used for conditions other than asthma	12 months

*Permitted when in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to visit one and throughout the study. Neither CPAP nor oxygen therapy may be initiated after Visit 1. Oxygen therapy described as resting oxygen therapy >3L/min (Oxygen use ≤3L/min flow is not exclusionary.)

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Screening and Critical Baseline Assessments

Subjects should conduct the pre-screening visit (Visit 0) up to 28 days prior to the screening visit (Visit 1). A subject number will be assigned at this time of signing informed consent. During the pre-screening Visit, study designated personnel should provide informed consent, and pharmacokinetics (PK) informed consent to potential study participants. Site staff will review with the subject any study related procedures that must be taken prior to the next visit (i.e., withholding of short-acting beta-2-agonists (SABAs), short-acting muscarinic antagonists (SAMAs) for 6 hours and withholding of asthma medication on the morning of Visit 1, etc).

7.1.1. Pre-screening Visit (Visit 0)

Subjects can complete the Pre-screening and Screening Visits on the same day.

Informed Consent will be obtained at the pre-screen visit. Once the informed consent process is complete and the informed consent document has been signed, additional pre-screening assessments can be conducted. The pre-screening assessments are defined in Section 1.2 and Table 1.

- Demographic information will be captured, including year of birth, gender, ethnic origin, race, height, and weight.
- Asthma history including asthma exacerbation history in previous year, asthma triggers, history of previous intubations.
- Therapy history including current treatment and courses of rescue corticosteroids.

7.1.2. Critical procedures performed at Screen (Visit 1)

- Medical history including but not limited to smoking status, aspirin sensitivity.
- Inclusion/exclusion criteria review
- Physical exam
- Pulmonary function tests and assessment of reversibility
- Vital signs
- Chest X-ray or if available review of chest X-ray/CT-scan conducted in the prior 6 months
- Resting 12 lead ECG
- The cardiovascular assessment (Appendix 5) will be administered by site personnel at screening visit. If the subject responds ‘yes’ to any of the questions a physician must conduct a further evaluation to assess for previously unrecognized and undiagnosed angina. The results of the evaluation should be considered when determining subject

eligibility (see Exclusion Criteria #5). Subject responses will be entered into the eCRF.

- Laboratory tests:
  - Haematology with differential
  - Clinical Chemistry
  - Urinalysis
  - Hepatitis B Surface Antigen and hepatitis C antibody
  - Urine pregnancy test for females of child bearing potential
  - FSH will be assessed to confirm child-bearing status as needed in women of non-child bearing potential only
- Parasitic screening will be performed only in subjects who have visited a high risk country

7.1.3. Critical procedures performed at randomization (Visit 2)

- Vital signs
- Review of randomization criteria, and data collected at screen including verification of eosinophilic asthma
- Pulmonary function tests and assessment of reversibility (If reversibility was not achieved at Visit 1, the procedure may be repeated at this visit and this is needed to qualify the subject for randomization). (See Section 7.2.4)
- Review eDiary data including PEF diurnal variability (see Section 7.2.2)
- Asthma Control Questionnaire (ACQ-5) (see Section 7.2.5)
- St George's Respiratory Questionnaire (SGRQ) (see Section 7.2.3)
- Laboratory tests:
  - Haematology with differential
  - Blood for baseline immunogenicity, PK
  - Urine pregnancy test for females of child bearing potential

7.2. Efficacy Assessments

Primary Efficacy Endpoint

Frequency of ***clinically significant exacerbations*** of asthma as defined by:

Worsening of asthma which requires use of systemic corticosteroids (SCS) [1]and/or hospitalisation and/or Emergency Department (ED) visits.

[1]*For all subjects, i.v. or oral corticosteroid (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For subjects on maintenance systemic corticosteroids (SCS)*, at least double the existing maintenance dose for at least 3 days is required.*

**Maintenance OCS is defined as a prescribed regimen of a minimum average daily dose of prednisone 5 mg (or equivalent).*

In order to provide an objective assessment of the circumstances linked to the clinical decision that defines asthma exacerbations, the investigator must take into account changes on one or more of the following parameters recorded in the subject's eDiary:

- Decrease in morning peak flow
- Increase in the use of rescue medication
- Increase in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use
- Increase in overall asthma symptom score

Secondary Efficacy Endpoints

- Time to first clinically significant exacerbation
- Mean change in St. George's Respiratory Questionnaire (SGRQ) at Week 52
- Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits over the 52-week treatment period
- Frequency of exacerbations requiring hospitalisation over the 52-week treatment period
- Mean change from baseline in clinic pre-bronchodilator FEV_1 at Week 52

Other Efficacy Endpoints

1. Mean change from baseline in Asthma Control Questionnaire (ACQ-5) score at Week 52
2. Percent of subjects evaluated as responders as measured by ACQ-5 score at Week 52.
3. Percent of subjects evaluated as responders as measured by SGRQ score at Week 52.
4. Percent of subjects recording a favourable treatment response as measured by the Subject Rated Response to Therapy at Week 52
5. Percent of subjects evaluated as having a favourable treatment response as measured by the Clinician Rated Response to Therapy at Week 52
6. Mean change from baseline in daily salbutamol/albuterol use
7. Mean change from baseline in daily asthma symptom scores
8. Mean change from baseline in awakening at night due to asthma symptoms requiring rescue medication use.
9. Mean change from baseline in morning PEF
10. Mean change from baseline in clinic post-bronchodilator FEV_1 at Week 52

11. Mean number of days with oral corticosteroids taken for clinically significant exacerbations
12. Total prednisone (or equivalent) exposure for clinically significant exacerbations over the 52-week treatment period
13. Frequency of all exacerbations
14. Time to first exacerbation
15. Time to withdrawal from study treatment due to asthma exacerbations
16. Time to first exacerbation requiring hospitalisation or ED visits
17. Unscheduled healthcare resource utilization (for clinically significant exacerbations and other asthma related health care) over the 52-week treatment period
18. Mean days of School/Work missed over the 52-week treatment period

7.2.1. Clinically Significant Exacerbations (primary endpoint)

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

Subjects will be asked to enter data on a daily basis into the eDiary. This data will be reviewed at each clinic visit by the site staff throughout the treatment period, during the clinic visit, to confirm an association between the exacerbation event and eDiary data.

The period of time for which exacerbation information will be included in the primary endpoint analysis will be from the start of treatment until approximately 4 weeks after the last dose of study medication. For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

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

7.2.2. eDiary Asthma Parameters and Alerts

The subject will be asked to record the following parameters daily in the eDiary from Visit 1 onwards:

- Morning peak flow (best of three), before rescue medication usage (L/min)

- Occasions of rescue usage over the previous 24-hours
- Asthma symptom score over the previous 24-hours using a 6-point scale (Appendix 6)
- Frequency of awakening due to asthma symptoms requiring rescue medication use.

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

For safety the following alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions to contact the investigator if any of the alert criteria are met. An alert in itself will not qualify as a clinically significant exacerbation:

- Decrease in morning PEF ≥30% on at least two of three successive days, compared with baseline (last 7 days of run-in).
- An increase of ≥50% in rescue medication on at least two of three successive days, compared with the average use for the previous week.
- Awakening due to asthma symptoms requiring rescue medication use for at least two of three successive nights.
- A symptom score of 5 for at least two of three successive days.

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

7.2.3. St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire is a well-established instrument, comprising 50 questions designed to measure Quality of Life in patients with diseases of airway obstruction [Jones, 1992]. The questionnaire will be administered at the visits specified in the Schedule of Activities (Section 1.2).
The questionnaire should be completed in a quiet area, free from distraction and the patient should ideally be sitting at a desk or table. Explain to the subject why they are completing it, and how important it is for clinicians and researchers to understand how their illness affects them and their daily life. Ask him or her to complete the questionnaire as honestly as they can and stress that there are no right or wrong answers, simply the answer that they feel best applies to them. Explain that they must answer every question and that someone will be close at hand to answer any queries about how to complete the questionnaire. It is designed for supervised self-administration. This means that the subject should complete the questionnaire themselves, but someone should be available to give advice if required. It is designed to elicit the subject's opinion of his/her health, ***not*** someone else's opinion of it, so family, friends or members of staff should not influence the subject's responses.

Once the subject has finished, it is very important that site staff check the questionnaire to make sure a response has been given to every question. If they have missed an item

return it to the subject for completion, *before they leave*. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaire and should be completed before any procedures are performed on the subject to avoid influencing the subject's response.

7.2.4. Pulmonary Function Testing including Reversibility

Spirometry will be conducted, using the site's own equipment at the visits specified in the Schedule of Activities (Section 1.2). The spirometer should meet American Thoracic Society standards and produce a printout of all data generated, which should be stored in the subject's notes. The spirometer should be calibrated in accordance with the manufacturer's instructions and a calibration log maintained. Spirometry must be performed at the same time (±2 hour) of the Visit 2 spirometry. Subjects should try to withhold SABAs or SAMAs for ≥6 hours and LABAs for ≥12 hours prior to clinic visit, if possible. Assessments to be recorded will include FEV_1, FVC. Pre-bronchodilator measurements will be taken at each clinic visit. In addition, at visit specified in the Schedule of Activities (Section 1.2) post-bronchodilator values will be recorded following standard reversibility testing. For subjects unable to achieve ≥12% reversibility and 200 mL change at Visit 1, reversibility can be repeated at Visit 2. Further details of spirometry and reversibility testing procedures are presented in the Study Reference Manual.

7.2.5. Asthma Control Questionnaire (ACQ)

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of a subject's asthma control that can be quickly and easily completed [Juniper, 2005]. The questions are designed to be self-completed by the subject. The five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze). The response options for all these questions consist of a zero (CCI [redacted]) to six (CCI [redacted]) scale.

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

It is recommended that the ACQ be administered at the same time during each visit. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaire and should be completed before any procedures are performed on the subject to avoid influencing the subject's response. Adequate time should be allowed to complete all items on the ACQ.

7.2.6. Clinician/Subject Rated Response to Therapy

The clinician and the subject will be asked to rate the response to therapy at the visits specified in the Schedule of Activities (Section 1.2). This is an overall evaluation of response to treatment, conducted separately by the investigator and the subject using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions: 1 = CCI; 2 = CCI; 3 = CCI; 4 = CCI; 5 = CCI; 6 = CCI; and 7 = CCI

7.3. Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 1.2). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Physical Examinations

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

A brief physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, and abdomen (liver and spleen). Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.3.2. Vital Signs

As detailed in the Schedule of Activities (Section 1.2), vital signs will be measured in sitting position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.

Vital signs assessments will be taken before measurement of any clinic lung function tests or ECGs at the specified time point.

7.3.3. Electrocardiogram (ECG)

A single twelve-lead ECG will be obtained at each timepoint specified in the Schedule of Activities (Section 1.2). If a routine single ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine whether the patient should be discontinued from the study. Refer to Section 5.5 for QTc withdrawal criteria.

ECG measurements will be made after the subject has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments but before lung function testing followed by other study procedures. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.

Paper ECG traces will be recorded at a standard paper speed of 25 mm/sec and gain of 10 mm/mV, with a lead II rhythm strip.

7.3.4. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 6, must be conducted in accordance with the Laboratory Manual, and Schedule of Activities Table. Laboratory requisition forms must be completed, and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

All blood samples which will be taken pre-injection, will be sent to a central laboratory for analysis (details provided in the Laboratory Manual). Standard reference ranges will be used.

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

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

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 6.

Table 6 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices:*	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatise	Albumin
Routine Urinalysis	Specific gravity pH, glucose, protein, blood and ketones by dipstick Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	Hepatitis B (HBsAg) Hepatitis C (Hep C antibody) FSH (as needed in women of non-child bearing potential only) Urine hCG Pregnancy test (as needed for women of child bearing potential) [2]
NOTES: 1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Appendix 2. 2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.	

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

To maintain the treatment blind, the site will not be sent information on haematology differential from any visits post-randomization either from the central laboratory or from GSK.

7.3.5. Immunogenicity

Blood samples will be collected for the determination of anti-mepolizumab antibodies, prior to dosing on dosing days, as detailed in the Schedule of Activities (Section 1.2). A PK sample will be collected at the time of the immunogenicity sample collection (for subjects in the PK sub-study this can be the sample collected for PK assessment). For subjects who are ADA or NAB positive, PK samples will be assessed.

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

7.4. Adverse Events and Serious Adverse Events

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

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.

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

- Any SAEs will be collected from the start of intervention until at the time points specified in the Schedule of Activities Table (Section 1.2).
- All AEs will be collected from the start of intervention until at the time points specified in the Schedule of Activities Table (Section 1.2).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent may 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 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek 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 subject has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

7.4.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 3.

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

7.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5). Further information on follow-up procedures is given in Appendix 3.

7.4.4. 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 product under clinical investigation. The sponsor will comply with country specific regulatory

requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

- Investigator safety reports are prepared for suspected unexpected serious adverse reactions(SUSAR) according to local regulatory requirements and sponsor policy and are forwarded to investigators as necessary.

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

7.4.5. Pregnancy

Details of all pregnancies in female subjects will be collected after the start of dosing and until 4 weeks post-last dose.

If a pregnancy is reported then the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

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

7.4.6. Cardiovascular and Death Events

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

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

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

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of mepolizumab plasma concentration will be collected as per the Section 1.2, Schedule of Activities Table. Samples should be obtained prior to dosing on dosing days. The actual date and exact time of each blood sample collection will be recorded in the eCRF.

Details for collection and processing of samples are provided in the Study Reference Manual (SRM).

7.5.2. Sample Analysis

Plasma analysis will be performed under the control of GSK PTS-DMPK/Scinovo, the details of which will be included in the Study Reference Manual. Concentrations of mepolizumab will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the Study Reference Manual).

7.6. Pharmacodynamics

Blood eosinophil counts will be recorded as part of standard haematological assessments performed at visits specified in the Schedule of Activities Table (Section 1.2). After Visit 2 blood eosinophil counts will be blinded to the Sponsor and site staff.

7.7. Health Outcomes

7.7.1. Health Outcome Endpoints

Mean days of school/work missed

Unscheduled healthcare resource utilization (for clinically significant exacerbations and other asthma related health care)

7.7.1.1. Mean days of school/work missed

The eDiary will be programmed to capture missed days of work/school.

7.7.2. Healthcare Resource Utilization

All unscheduled asthma-related health care utilization will be recorded including telephone contacts, specialist nurse visits, visits to a physician's office, home visits (day and night time), outpatient visits, visits to urgent care, visits to the emergency department, and hospitalizations associated with the subject's exacerbations will be recorded in the eCRF. Hospitalization data should be stratified by ward type (e.g; ICU, high dependency and usual care). Hospital length of stay in each type of ward will also be recorded.

The resource utilization paper worksheet used by the patient to record all health care contacts experienced since the last visit will be presented to the investigator (or designated coordinator) at the visits indicated in Table 1. The investigator (or designated coordinator) should ask the subject if any of the health care contacts that are recorded on the worksheet were due to an asthma exacerbation. The investigator can refer to his/her records to verify or supplement information given by the subject, if necessary.

If any unscheduled healthcare contact is due to an asthma exacerbation, then the asthma Exacerbation section of the eCRF must be completed.

Details regarding completion of the Healthcare Utilization worksheet are located in the SRM.

8. DATA MANAGEMENT

For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug.

CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This is a bridging study designed to determine the effect of Mepolizumab 100mg SC on clinically significant exacerbation events, compared with placebo among Chinese subjects.

The Chinese patient data collected in this study will be supplemented with data on the treatment effect for the same exacerbation endpoint from the global PhIII study MEA115588, using a Bayesian Dynamic Borrowing approach to analysis of the study (Schmidli, 2014). The potential to borrow information from the global dataset is based on the premise that the underlying disease, its general management and the response to mepolizumab is similar in Chinese and non-Chinese patients. A bridging approach is proposed because of the expected similarity of the treatment effect in Chinese patients and the global population (supported by similarities in the epidemiology, pathophysiology, pharmacology and clinical management of patients and consistency of treatment differences across key demographic factors including ethnicity), and similar study design specially the study population (supported by similarities in key eligibility criteria) between MEA115588 and this China study, hence there is low probability of the null effect being true.

A frequentist hypothesis test will not be performed. Instead, the posterior distributions of the primary endpoint, i.e. rate ratio of events between Mepolizumab 100mg SC vs. placebo will be derived based on the Bayesian analysis including the global PhIII study MEA115588 information and the data collected on Chinese patients in this study. The hypothesis of interest for treatment comparison is that the rate ratio is less than 1, and the study will be considered to have shown evidence that supports this hypothesis if the posterior probability that the rate ratio is less than 1 is at least 95% (a “positive result”). Please see the Appendix 9 for further information on the choice of posterior probability.

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

The sample size of 300 participants (considering 256 evaluable participants and additional 44 subjects for drop-out) in a 1:1 ratio has been determined by the superiority testing of mepolizumab 100 mg SC vs. placebo, there will be 90% power to detect a 40% decrease in the exacerbation rate from 1.7 per annum (p.a.) on placebo to 1.02 p.a. on mepolizumab 100mg SC using a two sided 5% significance level. The calculation assumes the number of exacerbations per year follows a negative binomial distribution [Keene, 2007] with a dispersion parameter k=0.8.

During the blinded evaluation, the clinically significant exacerbations which had occurred during the treatment period were analyzed using a generalized linear model assuming a negative binomial distribution and covariates of baseline maintenance OCS therapy (OCS vs. no OCS), EOS level at screening (>=300 cells/µL vs. <300 cells/µL), number of exacerbations in previous year (as an ordinal variable) and baseline disease severity (as % predicted FEV1). The blinded evaluation estimated, the overall event rate based on an assessment of blinded data was observed as 0.78 p.a., the dispersion was 2.0. This was lower than the expected overall event rate of the original study design assumptions.

This observed reduction for overall events at blinded evaluation can be explained by a reduction in exacerbation events during the COVID-19 pandemic, which was not unique in China, it is still expected that the treatment effect of Mepolizumab compared with placebo will be the same in Chinese SEA population as the original study design assumption. Therefore, according the formula [Friede, 2010]

$$\bar{\lambda} = (\lambda_T + \lambda_P)/2$$

where $\bar{\lambda}$ is the observed overall events rate based on an assement of blinded data, the λ_T and λ_P are the event rates in the treatment and placebo groups, and assuming the reduction in exacerbation rate with Mepolizumab will remain 40% under pandemic, the estimated event rates λ_T and λ_P for Mepolizumab 100mg SC and placebo are 0.975 and 0.585 p.a. respectively. On the other hand, there exists a difference for the estimate of dispersion when data is blinded or unblinded, so that the blinded dispersion estimate is adjusted by the difference between blinded and unblinded, which is 1.6=2.0 *(0.796 / 0.972), where the dispersion in MEA115588 study were 0.796 (unblinded) vs. 0.972 (blinded).

Therefore, based on the conclusion of the blinded evaluation, assuming a 40% decrease in the exacerbation rate from 0.975 per annum (p.a.) on placebo to 0.585 p.a. on mepolizumab 100mg SC will lead to a power of 66% implying a high false negative rate of 34% in China study. If there is a true reduction of 40% in exacerbation rate in Chinese patients, based on use of Bayesian dynamic borrowing with an initial weight of 0.5 on global MEA115588 study result, there will be 88.6% probability to achieve a positive result (equivalent to the power of the study).

The 40% reduction in exacerbation rate has been selected as reductions of this magnitude or greater have been seen in previous mepolizumab studies MEA112997 and MEA115588. However, it should be noted that a smaller reduction in exacerbations could be clinically significant. Under the same assumptions, there will be 99% probability of showing consistent trend, which is defined as the point estimation of rate ratio between Mepolizumab and placebo<1 in China study, with global MEA115588.

9.2.2. Sample Size Sensitivity

The sample size in Section 9.2.1 is based on an expected reduction in this rate for subjects treated with mepolizumab. If the expected reduction with mepolizumab differ then, at the given sample size there will be an effect on the probability of success of the study. Table 7 illustrates this effect on probability of success of varying reductions in rates with mepolizumab, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals from study treatment.

Table 7 Probability of meeting the success criterion conditional on various assumed true treatment effects

Reduction	45%	40%	35%	0
Probabilities of Success	94.6%	88.6%	80.0%	11.8%*

*The false positive rate is calculated as assumed true treatment effects is 0 between Mepolizumab and placebo.

In the Table 7 , the probabilities of meeting success are conducted under various assumed true treatment effects when overall event rate is fixed as 0.78 based on the blinded evaluation and dispersion is 1.6, e.g. when reduction is 40%, then the probability of success is calculated by the exacerbation rates for Mepolizumab 100mg SC and placebo as 0.975 and 0.585 p.a. respectively. Type I error is 11.8%, which is calculated when the event rate for each group is 0.78, adjusted dispersion is 1.6 based on analyses of blinded evaluation.

9.2.3. Sample Size Re-estimation or Adjustment

Blinded evaluation of exacerbation rates is planned for this study. A blinded evaluation of exacerbation rates for the purpose of sample size re-estimation will be done after 15 months of enrolment, or when 225 subjects have been randomized, whichever is earlier. If the exacerbation rates for the study are lower than planned, a sample size re-estimation may be conducted. Any subsequent change to the planned number of subjects randomized would be documented in a protocol amendment.

Prior to protocol amendment no 4, blinded evaluations of exacerbation rate indicated data that deviated substantially from the original assumptions for the study. These assumptions were based on data prior to the COVID-19 pandemic. The planned primary analyses is updated inorder to maintain the planned sample size without further adjustment.

9.3. Data Analysis Considerations

The following analysis populations will be derived as required.

9.3.1. Analysis Populations

- **All Subjects Enrolled Population**

The All Subjects Enrolled (ASE) Population will comprise all subjects enrolled and for whom a record exists on the study database. This population will be used summarizing reasons for screen and run-in failures.

- **Modified Intent-to-Treat Population**

The Modified Intent-to-Treat (MITT) population will consist of all randomized subjects who receive at least one dose of trial medication and will be the primary population for all analyses of efficacy and safety data. 'Modified' implies that subjects who were randomized but did not receive study treatment were excluded.

- **Per Protocol Population**

The Per Protocol (PP) population will consist of all subjects in the Modified Intent-to-Treat population not identified as full protocol deviators with respect to criteria that are considered to impact the primary efficacy analysis. The decision to exclude a subject from the PP Population or exclude part of their data from the PP Population analyses will be made prior to breaking the blind. This population will be used for a supplementary analysis of the primary endpoint.

- **PK Population**

The PK population will comprise subjects in the PK sub study who received at least one dose of study medication and for whom at least one pharmacokinetic sample was obtained, and analyzed. This will be the primary population for assessing PK.

9.3.2. Interim Analysis

Blinded evaluation of exacerbation rates is planned for this study. This will be done under blinded situation and will not treated as formal interim analysis.

No formal interim analysis is planned.

9.4. Key Elements of Analysis Plan

The primary treatment comparison of interest in the study is mepolizumab 100mg SC vs placebo. This treatment comparison will be made for the primary and secondary endpoints. There is no adjustment for multiplicity for the secondary endpoints.

9.4.1. Efficacy Analyses

Bayesian Dynamic Borrowing Design

Bayesian dynamic borrowing (BDB) provides a clinically and statistically rigorous method to analyze this China bridging study. An explicit, pre-specified belief about the relevance of the global MEA115588 results to the Chinese population on treatment effect is provided as part of the prior distribution, which is a mixture with two components, one reflecting results from MEA115588 study and a vague component reflecting 'no effect'.

The prior mixture will be upated with the China data to obtain the posterior distribution, which will also be a mixture. The posterior weight given to the global MEA115588 study data is commensurate with the strength of evidence of similarity between the MEA115588 data and the China data. The BDB analysis 'learns' how much of the global MEA115588 study information to borrow based on the consistency between the observed rate ratio in the China and global studies and updates the weight on the global MEA115588 results accordingly.

- The stronger the evidence of consistency, the greater the increase in the updated (posterior) weight on the informative component relative to the prior weight, and hence the greater the borrowing from the global study results.
- Conversely, if the China study results are very different to the global study results, the informative component is down-weighted and final inference is based mostly on the observed data in the China study alone.
- The mechanism by which the weight is updated is entirely pre-specified and mathematically rigorous (Schmidli, 2014)

The informative prior and prior weight in BDB design

The BDB approach will use the results from the global MEA115588 study mixed with a vague component worth two subjectsas an 'informative' but robust prior for the treatment comparison of interest in this China study. There are two primary analysis comparisons: mepolizumab 75mg IV vs placebo and mepolizumab 100mg SC vs placebo for rate of clinically significant exacerbations over the 32 weeks treatment period expressed as exacerbation rate per year in MEA115588. Since the primary outcome, rate of clinically significant exacerbation, showed similar treatment difference in Mepolizumab 75 mg iv group compared with placebo in 32-week Study MEA115588 and 52-week Study MEA112997, this indicates the available efficacy result of Mepolizumab 100 mg SC in 32-week study MEA115588 could also be an informative reference data to bridge to this 52-week China study using the same dose regimen, therefore, the results of mepolizumab 100mg SC vs placebo in study MEA115588 are used to build the global component.

Table 8 The primary analysis of clinically significant exacerbations results in global MEA115588 study

Treatment	No. subjects	Rate ratio (95% CI)	Normal distribution of Rate Ratio (log)	
			Mean	Standard Error
Mepolizumab 100mg SC	194	0.47 (0.35,0.64)	-0.7474	0.1532
Placebo	191			

Source: Table 13 in the CSR of MEA115588.

The logarithmic transformation of the rate ratio will be used, which can be approximately Normally distributed. Therefore, in the primary analysis for the primary treatment comparison of mepolizumab 100mg SC and placebo for the rate of clinically significant exacerbations of asthma over the 52-week treatment period in this study, the global prior component is obtained from the sampling distribution of the log rate ratio between mepolizumab 100mg SC and placebo in the global study MEA115588. The mean log rate ratio and its associated standard error are -0.7474 and 0.1532, respectively, leading to a normal distribution with mean -0.7474 and standard deviation 0.1532 as the global prior component for the primary treatment comparison.

A second vague distribution worth 2 subjects (one in each treatment arm) assuming no treatment effect in China will also be specified, to allow for the possibility that the global MEA115588 data do not provide relevant information about the treatment effect in Chinese patients. A normal distribution with mean zero and standard deviation 2.1256 will be used as vague prior for log rate ratio in BDB design, more details can be found in Appendix 9 Section 12.9.2. A weighted combination of the 'informative' and 'vague' priors will be used to construct a robust mixture prior.

In the primary analysis, a prior weight of 50% is proposed for the informative component of the robust mixture prior, with the remainder of the weight (50%) placed on the vague component to reflect a conservative starting position regarding the assumed relevance of the global MEA115588 results to Chinese patients. See Statistical Appendix 9 Section 12.9.2 for more details on the robust mixture prior and Section 12.9.3 for details on the choice of prior weight.

Effective Sample Size

The updated weight itself is not directly interpretable as the fraction of the global MEA115588 study sample size that is borrowed. Instead, the effective sample size (ESS) borrowed from the global study can be quantified using the moment method implemented in RBesT R software package version 1.6.1, Table 9 shows the expected value of the ESS borrowed from the global MEA115588 study for each treatment comparison when the true reduction in China is assumed to be 45%, 40%, 35% and 0 as the same with Table 8.

Table 9 Expected Effective Sample Size borrowed per arm from the global MEA115588 study for a range of possible true treatment differences

	The true reduction			
	0	35%	40%	45%
Expected value of ESS borrowed per arm from the global MEA115588 study	-42	76	123	162

Maximum Detectable Value for Rate Ratio

The maximum detectable value (MDV) is the maximum rate ratio that needs to be observed in this China study in order to meet the pre-specified success criteria when combined with the global MEA115588 study results via the Bayesian dynamic borrowing analysis. Under the current sample size of 300 participants in total (256 evaluable participants and 44 subjects for drop out), assuming overall event rate is 0.78 p.a. based on the blinded evaluation and dispersion is 1.6, chosen weight on global component in the mixture prior of 0.5, and success rule that the posterior probability of the true rate ratio in China being less than 1 is at least 95%, the MDV for rate ratio between mepolizumab and placebo is 0.776.That corresponds to a minimum detectable reduction for mepolizumab compared with placebo of at least 22.4%.

9.4.1.1. Primary Analyses

The primary treatment effect to be estimated in this study is the frequency of clinically significant exacerbations of asthma over the 52-week treatment period expressed as an exacerbation rate p.a. Exacerbations from the start of treatment until 4 weeks after the last dose of study drug will be used in the analysis. Exacerbations which are separated by less than 7 days will be treated as a continuation of the same exacerbation.

The numbers of clinically significant exacerbations are assumed to follow a negative binomial distribution. The logarithm of time on treatment will be used as an offset variable. The primary analysis of the rate of exacerbations will use a generalized linear model with a log-link function. This model will include covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), number of exacerbations in previous year (as an ordinal variable), baseline disease severity (as % predicted FEV1). The estimate of the logarithm of the rate ratio for mepolizumab vs. placebo and associated standard error will be the data used to update the robust mixture prior to obtain the final posterior distribution for the China rate ratio (on the log scale).

The mean, median and 90% credible interval of this posterior distribution of the rate ratio will be reported, along with the probability that true rate ratio is less than 1 (equivalent to the log rate ratio being less than 0).

The following 2-component mixture prior will be used for the log rate ratio:

$$p(\theta) = 0.5 * Normal(-0.7474\ , 0.1532) + 0.5 * Normal(0\ , 2.1256)$$

Sensitivity analysis will be conducted to assess the impact of different prior weights on the 'informative' component of the robust mixture prior, and the details will be specified in the RAP.

For the intercurrent event of withdrawal from study treatment, hypothetical strategy will be applied for primary analysis, where the logarithm of time on treatment will be used as an offset variable in the model.

The detailed missing data imputation method and supportive analysis will be defined in full RAP.

9.4.1.2. Key Secondary Analyses

- Time to first clinically significant exacerbations.
- Mean change in St. Georges Respiratory Questionnaire at Week 52
- Frequency of clinically significant exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits over the 52-week treatment period
- Frequency of clinically significant exacerbations requiring hospitalization over the 52-week treatment period
- Mean change from baseline in clinic pre-bronchodilator FEV1 at Week 52

Time to first clinically significant exacerbations will be analysed using Cox's proportional hazards model with covariates of treatment group, baseline maintenance OCS therapy, number of exacerbations in previous year (as an ordinal variable), baseline disease severity (as % predicted FEV1).

St. Georges Respiratory Questionnaire (SGRQ) score will be analysed using mixed repeated measures model adjusting for baseline maintenance OCS therapy, baseline SGRQ, number of exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, and treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.

The secondary endpoints of rate of exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits and rate of clinically significant exacerbations requiring hospitalization will be analyzed using negative binomial regression, as described for the primary endpoint above.

Pre-bronchodilator FEV1 will be analyzed using mixed effects repeated measures model adjusting for baseline maintenance OCS therapy, baseline FEV1, number of exacerbations in previous year (as an ordinal variable), and treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group.

The point estimate as well as the estimate of the variability in above analyses will be provided. More details will be provided in full RAP.

9.4.1.3. Other Analyses

Full details of the analyses to be performed on other efficacy endpoints will be given in the RAP.

9.4.2. Safety analyses

The MITT- population will be used for the analysis of safety data. 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 subjects administered investigational 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 Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary and summarized by preferred term and treatment group. AEs and SAEs occurring pre-treatment, during active treatment and post-treatment will be summarized separately. The number and percentage of subjects experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug-related AEs, SAEs, events of special interest (including systemic reactions and local injection site reactions) and for AEs leading to permanent discontinuation of study drug or withdrawal from the study. Additional analyses to fully describe events of special interest will be defined in the RAP.

9.4.2.3. Clinical Laboratory Evaluations

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

Actual values and change from baseline for other scheduled safety assessments such as vital signs (pulse rate, systolic and diastolic blood pressure), 12-lead ECG parameters (QTc and heart rate) will be summarized at each scheduled visit. Further details will be provided in the RAP.

9.4.2.5. Immunogenicity

Immunogenicity will be summarized using appropriate descriptive statistics.

9.4.3. Pharmacokinetic Analyses

Blood samples will be collected to determine mepolizumab plasma concentrations at Visits specified in the Table 1 (Section 1.2). The mepolizumab plasma concentrations from this study will be analyzed using non-compartmental analysis and/or population PK analysis approach. When population PK analysis is considered necessary, it will be conducted using, for example, NONMEM 7 for determination of the population and/or individual systemic exposure, volume of distribution and clearance as well as characterise the between- and within subject variability. The effect of subjects' characteristics such as body weight, age, gender, serum creatinine on mepolizumab systemic exposure will also be explored in order to explain the inter-subject variability in drug exposure. Population PK analysis may incorporate previous Caucasian PK data to explore the potential ethnic difference between Chinese and Caucasians in mepolizumab exposure. Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively.

9.4.4. Pharmacodynamic Analyses

Blood eosinophil ratio to baseline will be analysed using mixed model repeated measures adjusting for baseline, baseline maintenance OCS therapy, number of exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, and treatment, visit, visit by baseline interaction and visit by treatment group interaction. Data will be log-transformed prior to analysis. Values of zero will be imputed as half the lowest observed value for that measure within the entire study database prior to the log transformation.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate, details of any PK/PD analyses to be performed will be given in the RAP.

9.4.6. Health Outcome Analyses

Details of the analyses to be performed on the health outcome endpoints listed in Section 7.7 will be given in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

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

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

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

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

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

If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

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

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse Event
ALT	Alanine transaminase
AST	Aspartate transaminase
ATS	American Thoracic Society
CPAP	Continuous Positive Airway Pressure
CS	Corticosteroid
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case report form
ED	Emergency Department
eDiary	Electronic diary
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
IDMC	Independent Data Monitoring Committee
ICS	Inhaled corticosteroids
ICU	Intensive Care Unit
IEC	Independent ethics committee
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
IP	Investigational Product
IRB	Institutional review board
ITT	Intent to Treat
IUD	Intrauterine Device
IV	Intravenous
IWRS	Interactive web response system
LABA	Long-acting beta-2-agonists
LTRA	Leukotriene receptor antagonist
MedDRA	Medicinal dictionary for regulatory activities
mcg	Micrograms
MDI	Metered Dose Inhaler
mg	Milligram
N/A	Not applicable

NHLBI	National Heart Lung and Blood Institute
OCS	Oral corticosteroids
p.a.	Per annum
PEF	Peak expiratory flow
PK	Pharmacokinetic
RAP	Reporting and Analysis Plan
SABA	Short-acting beta-2-agonist
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonist
SC	Subcutaneous
SCS	Systemic corticosteroids
SGRQ	St. George's Respiratory Questionnaire
SRM	Study reference manual
ULN	Upper Limit of Normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
RAMOS NG
Seretide

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA
Xolair

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

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV 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, if INR measured
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 and Follow up Assessments	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • 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 unless allowed per protocol	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B DNA and Hepatitis delta antibody[5]. • Obtain blood sample for pharmacokinetic (PK) analysis, within 28 days after last dose[6]

and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments	• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page
MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • 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 perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	**<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 treatment 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, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding**

studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to 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 IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If Hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of Hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • 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.

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

12.3.1. Definition of Adverse Events

Adverse Event 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> AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement 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 treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 overdose should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

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 subject’s condition.

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

12.3.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
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, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

12.3.3. Definition of Cardiovascular Events

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

12.3.4. Recording of AEs and SAEs

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

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

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

12.3.5. Reporting of SAEs 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) and fax the form to GSK within 24 hours.**
- **The site will enter the SAE data into the electronic system as soon as it becomes available.**
- **The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.**

- **After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.**
- **If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.**
- **Contacts for SAE reporting can be found in SPM.**

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 SPM.

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

12.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

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

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

Woman 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).
- 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.

12.4.2. Contraception Guidance

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in below:

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 *(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.)*
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 *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Hormonal contraception may be susceptible to interaction with other medications, which may reduce the efficacy of the contraceptive method.

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 for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

12.4.3. Collection of Pregnancy Information:

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue mepolizumab.

Based on the absence of an identified reproductive hazard from preclinical studies, absence of a genotoxic potential, and very low levels of mepolizumab that might be present in semen, there is no recognized risk for mepolizumab to affect human sperm or the fetus if transferred to a female partner via semen. Therefore, the use of condoms or other methods of contraception in the male study subject is not required.

12.5. Appendix 5: Cardiovascular Screening Questions

At screening each subject should be asked the following:

Unrelated to the symptoms you experience with your asthma:

Do you have any pain or discomfort (such as pressure) in your chest?

If yes, does this pain/discomfort/pressure go to other areas of your body such as neck, jaw, throat, or down your arms (including a numbness feeling in your arm) when it occurs?

When you walk at an ordinary pace on a level surface does this produce chest pain? If yes, respond to a and b:

Does this chest pain or discomfort occur when you are not doing any activities such as resting in bed or sitting in a chair?

Has this chest pain/discomfort been more frequent or more intense or last longer or come on with less exertion lately?

When you walk uphill or hurry does this produce chest pain/discomfort?

Do you use or have you been previously prescribed nitroglycerine to relieve the discomfort?

If yes, have you needed to increase the number of pills or frequency of using the pills recently?

If the subject responds "yes" to any of the above questions a study physician should further assess for the presence of undiagnosed or unrecognized angina when evaluating Exclusion Criteria 5.

12.6. Appendix 6: Daily Asthma Symptom Score

Each morning subjects will record an asthma symptom score using the following scale:

- Daily Symptom Score:

  0 = CCI [redacted]

  1 = CCI [redacted].

  2 = CCI [redacted]

  3 = CCI [redacted]

  4 = CCI [redacted]

  5 = CCI [redacted]

12.7. Appendix 7: 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 hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
   a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

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

12.8. Appendix 8: New York Heart Association Functional Classification of Congestive Heart Failure

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

12.9. Appendix 9 Statistical Appendix

12.9.1. Choice of posterior probability

A 95% posterior probability that the true rate ratio < 1 represents a high level of confidence for declaring a positive treatment benefit in Chinese patients in the context of a bridging study where substantial evidence of treatment benefit in global (non-Chinese) patients already exists and is aligned with examples of Bayesian decision criteria given in the FDA draft guidance on Complex Innovative Designs [https://www.fda.gov/media/130897/download]. This represents a more rigorous evidentiary threshold than is typically provided by a 'positive trend 'design, which requires only that the observed rate ratio < 1.

12.9.2. Overview of the proposed robust mixture prior and analysis strategy

In order to formally incorporate the global MEA115588 study data in this study, the Bayesian analysis with a robust mixture prior distribution [Schmidli, 2014], which allows for "dynamic borrowing" of prior information, will be conducted. This analysis learns how much of the global prior information to borrow based on the consistency between the China data and global prior. The mixture prior was constructed by two components.

- Component 1 is an informative prior based on the observed efficacy response from global study MEA115588, referred to as the "global prior"
- Component 2 is a "vague" prior centred on a mean of zero and with variance scaled to represent information equivalent to one subject

Denoting the log rate ratio for Mepolizumab 100mg SC vs. placebo as θ, the prior has the form

$$p(\theta) = w * p_1(\theta) + (1 - w) * p_2(\theta)$$

where $p_1(\theta)$ is the component containing the information from the global study prior, $p_2(\theta)$ is the vague component and w is the weight.

The prior weight w assigned to the informative prior component represents the prior degree of confidence in the extrapolation strategy. At lower prior weight the mixture prior presents a heavier tailed distribution with more prior weight being applied to the non-informative vagueprior component. When the mixture prior is combined with the observed global data, w is updated according to how consistent China data are with the global prior: the stronger the evidence of consistency, the greater the increase in the posterior weight w^* relative to the prior weight w. Conversely, when there is prior-data conflict, w^* will be lower than w and will tend to zero as evidence of conflict increases, so that the global information is down-weighted and posterior inference is based almost entirely on the China data.

12.9.2.1. The informative (global) prior

The global prior distribution was constructed using a normal approximation to the sampling distribution of the observed log rate ratio of exacerbations on mepolizumab vs. placebo in the subjects from global study MEA115588. The point estimation and standard error for the log rate ratio obtained from negative binomial regression of the observed exacerbation counts were used as the mean and standard deviation, respectively, of a normal prior distribution for the global efficacy response. Therefore, based on the results in global MEA115588 presented in Table 8, it provided a Normal $(-0.7474, 0.1532^2)$ as the global prior for log rate ratio.

12.9.2.2. The vague prior

The vague prior has a mean of 0 for rate ratio on log scale (i.e. no effect in China), and the variance is scaled such that the information content of the prior is approximately equivalent to that provided by two subjects, one subject per arm. This variance was determined by taking the squared standard error of the log rate ratio obtained from the global data and multiplying it by N/2, where N is the total MEA115588 sample size. Therefore, the SD of the vague prior is

$$SD = \sqrt{0.1532^2 * \frac{385}{2}} = 2.1256$$

12.9.2.3. Initial weight on informative (global) prior component and mixture prior

An initial (prior) weight of 50% is proposed for the informative global component of the robust mixture prior, with the remainder of the weight (50%) placed on the vague prior to reflect a conservative starting position regarding the assumed relevance of the global MEA115588 results to Chinese. Combining the two components and their respective weights gives the following 2-component mixture normal:

$$p(\theta) = 0.5 * Normal(-0.7474\,, 0.1532) + 0.5 * Normal(0\,, 2.1256)$$

12.9.3. Choice of weights

The scientific grounds for expecting similar benefit: risk profile in China and global study patients justifies a high initial weight on the informative component. However, based on an extensive review of the impact of the prior weight specified for the global MEA115588 study (prior weights explored were: 0, 0.1, 0.2, …0.9,1), a more conservative prior weight of 50% was felt to provide an acceptable trade-off between the risks of a false positive result and a false negative result, and to enable meaningful gains in precision due to borrowing information from the global study whilst ensuring that the prior does not dominate the posterior completely but allows the observed data in Chinese patients to contribute to the inference from the study.

12.10. Appendix 10: Protocol Amendment Changes

12.10.1. Protocol Amendment 1

This amendment applies to all sites participating in Study 201536.

Rationale

This protocol amendment is being implemented to update Medical Monitor Name and Contact Information, clarify inclusion criteria/exclusion criteria, randomization criteria, withdrawal/stopping criteria, subject and study completion, concomitant therapy, efficacy assessments and other minor protocol clarifications.

The following revisions were made:

- Medical Monitor Name and Contact Information updated
- Inclusion criteria updated: controller Medication clarified
- Withdrawal/stopping criteria updated: withdrawal from study treatment and withdrawal from study clarified
- Subject and study completion clarified
- Concomitant therapy updated: additional asthma medication treatment clarified
- Efficacy assessments updated: treatment duration clarified
- Editing or typo errors revised
- Synopsis updated based on main text update
- References updated

List of Specific Changes

Section: Medical Monitor Name and Contact Information

Original text:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	Tel: PPD PPD	PPD	PPD	Tower A, Ocean International Center no. 56, Mid 4th East Ring Rd. Beijing.100025
Secondary Medical Monitor	PPD	PPD PPD	PPD	PPD	Tower A, Ocean International Center no. 56, Mid 4th East Ring Rd. Beijing.100025
SAE		PPD		PPD	No. 1 Building, 917 Halei Road, Pudong, Shanghai, 201203, China

Amendment text:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	***Tel:***PPD PPD	PPD	PPD	***Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China***
Secondary Medical Monitor	PPD	PPD	PPD	PPD	***Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China***

SAE		PPD		PPD	***Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China***

Synopsis: Objectives and Endpoints/ Section: 3. OBJECTIVES AND ENDPOINTS: other Endpoints/section 7.2. Efficacy Assessments: Other Efficacy Endpoints

Original text:

15.Time to withdrawal due to asthma exacerbations

Amendment text:

15. Time to withdrawal ***from study treatment*** due to asthma exacerbations

section: synopsis: Treatment Arms and Duration

Original text:

Following screening to assess eligibility and a run-in period for 1-4 weeks during which baseline data will be captured in an eDiary, subjects will be randomized in a 1:1 ratio to receive either mepolizumab (100 mg) SC or placebo SC added onto their existing therapy for asthma every 4 weeks for a total of 13 doses. The treatment period will conclude with subjects completing Exit Visit assessments approximately 4 weeks after the last dose. An early withdrawal visit should be conducted within 4 weeks of the last dose received.

Amendment text:

Following screening to assess eligibility and a run-in period for 1-4 weeks during which baseline data will be captured in an eDiary, subjects will be randomized in a 1:1 ratio to receive either mepolizumab (100 mg) SC or placebo SC added onto their existing therapy for asthma every 4 weeks for a total of 13 doses. The treatment period will conclude ~~with subjects completing Exit Visit assessments~~ approximately 4 weeks after the last dose. ~~An early withdrawal should be conducted within 4 weeks of the last dose received.~~

Section: Synopsis: Treatment Arms and Duration/ 4.2. Treatment Arms and Duration/ section:6.2. Study Treatment Assignment

Original text:

Subjects will be stratified based on blood eosinophil count at screening (≥300 cells/μL and <300 cells/μL). A minimum of 150 subjects will be enrolled with blood eosinophil count ≥300 cells/μL.

Amendment text:

Subjects will be stratified based on blood eosinophil count at screening (≥300 cells/μL ~~and~~ **,** <300 cells/μL). A minimum of 150 subjects will be enrolled with blood eosinophil count ≥300 cells/μL.

Section: synopsis: Table 1 Schedule of Activities Table

Original text:

Procedures	**Pre-screening**	**Screen/Run-in**	**Randomised Treatment (visit window is ± 7 days for V3-15 V2-1, V2-2, V14, V14-1, V14-2 visit window is ± 2 days from V2 or V14 in sub-study)**	**Exit Visit**	**With-drawal**

Amendment text:

Procedures	**Pre-screening**	**Screen/Run-in**	**Randomised Treatment (visit window is ± 7 days for V3-~~15~~*V15-2;* V2-1, V2-2~~, V14~~, V14-1, V14-2 visit window is ± 2 days from V2 or V14 in sub-study)**	**Exit Visit**	**With-drawal**

Original text:

Study Day		**-28~-7**	**1**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**343**	**350**	**364**	**392**	**480**	
Hepatitis B and C testing[13, 14]		**X**																					

19. If hepatitis C positive confirmation by testing the same sample is required. See central laboratory manual for details. For subjects who are HBsAg positive or HBcAb positive reflexive testing must be conducted to assess HBV DNA.
20. If ALT ≥3X ULN, reflexive testing should be conducted for HBV-DNA.

Amendment text:

Study Day		**-28~-7**	**1**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**343**	**350**	**364**	**392**	**480**	
Hepatitis B and C testing[13, 14]		**X**																					

13. If hepatitis C positive confirmation by testing the same sample is required. See central laboratory manual for details. ~~For subjects who are HBsAg positive or HBcAb positive reflexive testing must be conducted to assess HBV DNA.~~

14. ~~If ALT ≥3X ULN, reflexive testing should be conducted for HBV DNA.~~ ***For subjects who are HBsAg positive at Visit 1 or HBcAb positive (documented previous positive result) reflexive testing must be conducted to assess HBV DNA.***

Section 4.2. Treatment Arms and Duration: Table 4

Original text

Phase	Phase Title	Duration	Description
3	Treatment	52 weeks	At Visit 2 (Week 0) those subjects who successfully complete the run-in period as well as meet the pre-defined randomization criteria will be randomized; those subjects that do not meet the pre-defined randomization criteria will be deemed run-in failures (see Section 5.4). Study medication will be administered SC every 4 weeks for a total of 13 doses (Visit 2 to Visit 14, inclusive). The treatment period will conclude with subjects completing Exit Visit or Early Withdrawal Visit assessments approximately 4 weeks after the subject was administered their last dose of double-blind study treatment (i.e. at Week 52). PK samples will be collected at Week 0, 1, 2, 4, 24, and Week 48, 49, 50, 52, 56, 60 (or 0, 1, 2, 4, 8, 12 weeks after last dose) in subjects who provided consents for PK sub-study.

Third: Amendment text:

Phase	Phase Title	Duration	Description
3	Treatment	52 weeks	At Visit 2 (Week 0) those subjects who successfully complete the run-in period as well as meet the pre-defined randomization criteria will be randomized; those subjects that do not meet the pre-defined randomization criteria will be deemed run-in failures (see Section 5.4). Study medication will be administered SC every 4 weeks for a total of 13 doses (Visit 2 to Visit 14, inclusive). The treatment period will conclude ~~with subjects completing Exit Visit or Early Withdrawal Visit assessments~~ approximately 4 weeks after the subject was administered

Phase	Phase Title	Duration	Description
			their last dose of double-blind study treatment ~~(i.e. at Week 52)~~. PK samples will be collected at Week 0, 1, 2, 4, 24, and Week 48, 49, 50, 52, 56, 60 (or 0, 1, 2, 4, 8, 12 weeks after last dose) in subjects who provided consents for PK sub-study.

First: section 5.1. Inclusion Criteria

Second: Original text

19. **Controller Medication:** Current treatment with an additional controller medication, besides ICS, for at least 3 months. [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline]

Third: Amendment text:

6. **Controller Medication:** Current treatment with ~~an~~ **one** ***or more*** additional controller medication, besides ICS. ***At least one additional controller medication must have been regularly used*** for at least 3 months ***prior to Visit 1.*** [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline]

First: section 5.2. Exclusion Criteria

Second: Original text

3. **Chest X-ray:** A chest X-ray that reveals evidence of clinically significant abnormalities not believed to be due to the presence of asthma.

Third: Amendment text:

3. **Abnormal Chest X-ray (or CT scan):** A chest X-ray **(or CT scan)** that reveals evidence of clinically significant abnormalities not believed to be due to the presence of asthma. **If a chest X-ray (or CT scan) is not available within 6 months prior to Visit 1, then a chest X-ray must be conducted.**

First: section 5.3. Randomization Criteria

Second: Original text

5. **Abnormal clinically significant finding**: Subjects have had clinically significant findings in their laboratory screening tests including liver chemistry at Visit 1.

Third: Amendment text:

5. **Abnormal clinically significant finding**: Subjects have ~~had~~ ***no evidence of*** clinically significant findings in their laboratory screening tests including liver chemistry at Visit 1.

First: section 5.5. Withdrawal/Stopping Criteria

Second: Original text

Subjects may be withdrawn from study treatment at anytime by the Investigator if it is considered to be detrimental for them to continue in the study. Reasons for withdrawal can include: an adverse event (including abnormal liver function test or abnormal laboratory results), Investigator unblinded study treatment, clinically significant abnormality identified on ECG reading, lost to follow-up, protocol violation, lack of efficacy, sponsor terminated study, non-compliance, pregnancy, or for any other reason.

Subjects are also free to withdraw consent to participate in the study at anytime. Every effort should be made to have them return to the clinic for an Early Withdrawal Visit and to return all study related materials. In those instances where the subject specifies the reason for withdrawal of consent, this information will be captured in the eCRF.

Subjects who withdraw from study treatment prematurely (for any reason) should , where possible, continue to be followed-up as per protocol until the completion of the Exist Visit assessments. If this is not possible, the Investigator must encourage the subject to participate in as much of the study as they are willing (or able) to. Further information are provided in the Study Reference Manual (SRM).

A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

In the event a subject withdraws at, or during, a scheduled visit, and does not receive investigational product, an Early Withdrawal Visit is not required. However, all study procedures scheduled at an Early Withdrawal Visit must be performed at this visit instead.

The primary reason for withdrawal will be recorded in the eCRF and any data collected up until the point of withdrawal will be used in the analyses.

Third: Amendment text:

Withdrawal from study treatment

Subjects may be withdrawn from study treatment at anytime by the Investigator if it is considered to be detrimental for them to continue in ~~the~~ study ***treatment***.

A subject must be withdrawn from study treatment if any of the following stopping criteria are met:

- ***Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria (section 5.5.1)***
- ***QT: Meets any of the protocol-defined stopping criteria (section 5.5.2)***
- ***Pregnancy: Positive pregnancy test***

Other r~~R~~easons for withdrawal can include: an adverse event (including abnormal liver function test ***other than stopping criteria*** or abnormal laboratory results), Investigator unblinded study treatment, clinically significant abnormality identified on ECG reading ***other than stopping criteria***, lost to follow-up, protocol violation, lack of efficacy, sponsor terminated study, non-compliance, ~~pregnancy,~~ or for any other reason

Subjects who withdraw from study treatment prematurely (for any reason) should, where possible, continue to be followed-up as per protocol until the completion of the Visit assessments. If this is not possible, the Investigator must encourage the subject to participate in as much of the study ***(scheduled visits and activities, record eDiary data)*** as they are willing (or able) to. ***If subject cannot attend the visit on site, telephone contact is acceptable to collect below information: asthma exacerbation, AE/SAE, concomitant medication and to encourage subjects continue to record eDiary data.*** ~~Further information are provided in the Study Reference Manual (SRM).~~

Withdrawal from the study

Subjects are also free to withdraw consent to participate in the study at anytime. Every effort should be made to have them return to the clinic for an Early Withdrawal Visit and to return all study related materials. In those instances where the subject specifies the reason for withdrawal of consent, this information will be captured in the eCRF. ***Patients will not be followed for any reason after consent has been withdrawn.***

A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

In the event a subject withdraws ***from study*** at, or during, a scheduled visit, and does not receive investigational product, an Early Withdrawal Visit is not required. However, all study procedures scheduled at an Early Withdrawal Visit must be performed at this visit instead.

The primary reason for withdrawal ***from study*** will be recorded in the eCRF and any data collected up until the point of withdrawal ***from study*** will be used in the analyses ***when appropriate***.

First: section 5.6. Subject and Study Completion

Second: Original text

Subjects will be regarded as having completed the study if they complete all phases of the study (run-in, double-blind treatment administration, and Exit Visit).

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

Third: Amendment text:

Subjects will be regarded as having completed the study if they complete all phases of the study (run-in, double-blind treatment administration, and Exit Visit) ***OR although they prematurely discontinue study treatment but still complete the Week 52 Visit***.

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

First: section 6.9.1. Permitted Medications and Non-Drug Therapies

Second: Original text

All concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. However, for OCS, the dose must be recorded as well as any dose changes.

Additional asthma medications such as theophyllines or anti-leukotrienes will be permitted provided they have been taken regularly in the 3 months prior to randomization (Visit 2, Week 0).

……

Third: Amendment text:

All concomitant medications taken during the study will be recorded in the eCRF ***as well as the ICS usage in the past 12 months prior to Visit 1 and other additional controllers in the past 3 months prior to Visit 1***. The minimum requirement is that drug name and the dates of administration are to be recorded. However, for ***ICS and*** OCS, the dose must be recorded as well as any dose changes.

All additional asthma medications such as ***LABA***, theophyllines or anti-leukotrienes will be ~~permitted provided~~ ***continually used with the same dose and regimen*** if they have been taken regularly in the 3 months prior to randomization (Visit 2, Week 0).

If for any reasons (except asthma exacerbation) the participant must change their maintenance asthma treatment medications, the investigator must discuss the change

with the Medical Monitor prior. Any changes of maintenance asthma treatment should be recorded in the eCRF.

First: section 7.1.2. Critical procedures performed at Screen (Visit 1)

Second: Original text

- ……
- Vital signs
- Resting 12 lead ECG
- ……

Third: Amendment text:

- ……
- Vital signs
- ***Chest X-ray or if available review of chest X-ray/CT-scan conducted in the prior 6 months.***
- Resting 12 lead ECG
- ……

First: section 7.2 Other Efficacy Endpoints

Second: Original text

15. Time to withdrawal due to asthma exacerbations

Third: Amendment text:

15. Time to withdrawal **from study treatment** due to asthma exacerbations

First: section 7.2.1. Clinically Significant Exacerbations (primary endpoint)

Second: Original text

……

The period of time for which exacerbation information will be included in the primary endpoint analysis will be from the start of treatment until the Week 52 visit approximately 4 weeks after the last dose of study medication. For those subjects that early withdraw, the time period for primary endpoint collection will be from the start of

treatment until the date of withdrawal (but no greater than approximately 4 weeks post last dose) For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

……

Third: Amendment text:

……

The period of time for which exacerbation information will be included in the primary endpoint analysis will be from the start of treatment until ~~the Week 52 visit~~ approximately 4 weeks after the last dose of study medication. ~~For those subjects that early withdraw, the time period for primary endpoint collection will be from the start of treatment until the date of withdrawal (but no greater than approximately 4 weeks post last dose)~~ For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

……

First: section 7.2.3. St. George's Respiratory Questionnaire (SGRQ)

Second: Original text

……The questionnaire will be administered at baseline (Visit 2) and at the Exit Visit.

Third: Amendment text:

…… The questionnaire will be administered at ~~baseline (Visit 2) and at the Exit Visit~~ ***visits specified in the Schedule of Activities (Section 1.2).***

First: section 7.2.4. Pulmonary Function Testing including Reversibility

Second: Original text

…… Spirometry must be performed at the same time (±1 hour) of the Visit 2 spirometry. Subjects should try to withhold SABAs or SAMAs for ≥6 hours and LABAs for ≥12 hours prior to clinic visit, if possible. Assessments to be recorded will include FEV_1, FVC and PEF. Pre-bronchodilator measurements will be taken at each clinic visit. ……

Third: Amendment text:

…… Spirometry must be performed at the same time (±~~1~~***2*** hour) of the Visit 2 spirometry. Subjects should try to withhold SABAs or SAMAs for ≥6 hours and LABAs for ≥12 hours prior to clinic visit, if possible. Assessments to be recorded will include FEV_1, FVC ~~and PEF~~. Pre-bronchodilator measurements will be taken at each clinic visit. ……

First: section 7.4.5. Pregnancy

Second: Original text

Details of all pregnancies in female subjects will be collected after the start of dosing and until 4 weeks post-last dose.

Third: Amendment text:

Details of all pregnancies in female subjects will be collected after the start of dosing and until 4 ~~weeks~~***months*** post-last dose.

First: section 9.2.1. Sample Size Assumptions

Second: Original text

……

To account for the loss of patient years data from subjects who withdraw early from the trial, additional 44 subjects (22 in the mepolizumab treatment arm and 22 in the placebo treatment arm) will be randomized; ……

Third: Amendment text:

……

To account for the loss of patient years data from subjects who withdraw ~~early from the trial~~ ***from study treatment early***, additional 44 subjects (22 in the mepolizumab treatment arm and 22 in the placebo treatment arm) will be randomized; ……

First: section 9.2.2. Sample Size Sensitivity

Second: Original text

……Table 7 illustrates this effect on power of varying placebo rates and reductions in rates with mepolizumab, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals, and a dispersion parameter k=0.8.

……

Table 8 illustrates the estimated power which would be obtained with different dispersion parameter, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals, and the placebo and mepolizumab rates are 1.7 and 1.02

respectively. It also shows the estimated sample size which would be required for 90% power.

……

* Early withdrawal is not taken into account.

Third: Amendment text:

…… Table 7 illustrates this effect on power of varying placebo rates and reductions in rates with mepolizumab, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals ***from study treatment***, and a dispersion parameter k=0.8.

……

Table 8 illustrates the estimated power which would be obtained with different dispersion parameter, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals ***from study treatment***, and the placebo and mepolizumab rates are 1.7 and 1.02 respectively. It also shows the estimated sample size which would be required for 90% power.

……

*Early withdrawal ***from study treatment*** is not taken into account

12.10.2. Protocol Amendment 2

This amendment applies to all sites participating in Study 201536.

Rationale

This protocol amendment is being implemented to update inclusion criteria 3#, switching FEV1 predicted value equation from NHANESIII to Quanjer2012, updeated related content in pulmonary function testing section, reference and abbreviation accordingly.

The following revisions were made:

- Inclusion criteria updated: FEV1
- Pulmonary Function Testing including Reversibility updated: NHANES III value
- References updated
- Abbreviations updated

- Editing or typo errors revised

List of Specific Changes:

Section: Table 1 Schedule of Activities Table

Original text

Visit	**V0[1]**	**V1**	**V2[2]**	**V 2-1[3]**	**V 2-2[3]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V 14-1[3]**	**V 14-2[3]**	**V15**	**V 15-1[3]**	**V 15-2[3]**	
Study Week		**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**49**	**50**	**52**	**56**	**60**	
Study Day		**-28~-7**	**1**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**343**	**350**	**364**	**392**	**480**	
Register Visit in RAMOS/IWRS	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X			X			X
Complete electronic Case Report Form (eCRF)		X	X			X	X	X	X	X	X	X	X	X	X	X	X			X			X

Amendment text:

Visit	**V01**	**V1**	**V22**	**V 2-1[3]**	**V 2-2[3]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V 14-1[3]**	**V 14-2[3]**	**V15**	**V 15-1[3]**	**V 15-2[3]**	
Study Week		**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**49**	**50**	**52**	**56**	**60**	
Study Day		**-28~-7**	**1**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**343**	**350**	**364**	**392**	~~**480**~~**420**	
Register Visit in RAMOS/IWRS	X	X	X	***X***	***X***	X	X	X	X	X	X	X	X	X	X	X	X	***X***	***X***	X	***X***	***X***	X
Complete electronic Case Report Form (eCRF)	***X***	X	X	***X***	***X***	X	X	X	X	X	X	X	X	X	X	X	X	***X***	***X***	X	***X***	***X***	X

Section 5.1. Inclusion Criteria

Original text

3. **FEV_1**: Persistent airflow obstruction as indicated by:
    - For subjects ≥18 years of age at visit 1, a pre-bronchodilator FEV_1 <80% predicted (NHANES III)
    - For subjects 12-17 years of age at visit 1:

• A pre-bronchodilator FEV_1 <90% predicted (NHANES III) recorded at Visit 1 OR

• FEV_1: FVC ratio <0.8 recorded at visit 1

Amendment text:

4. **FEV_1**: Persistent airflow obstruction as indicated by:

- For subjects ≥18 years of age at visit 1, a pre-bronchodilator FEV_1 <80% predicted ~~(NHANES III)~~ ***normal values calculated by Quanjer reference equations [Quanjer, 2012]***
- For subjects 12-17 years of age at visit 1:

  • A pre-bronchodilator FEV_1 <90% predicted (~~NHANES III~~ ***Quanjer,2012***) recorded at Visit 1 OR

  • FEV_1: FVC ratio <0.8 recorded at visit 1

Section 7.2.4. Pulmonary Function Testing including Reversibility

Original text

……Further details of spirometry and reversibility testing procedures are presented in the Study Reference Manual. For predicted FEV_1 values, NHANES III values will be used and adjustments to these values will be mande for race [Hankinson,2010]. Asian equations will be used.

Amendment text:

……Further details of spirometry and reversibility testing procedures are presented in the Study Reference Manual. ~~For predicted FEV_1 values, NHANES III values will be used and adjustments to these values will be mande for race [Hankinson,2010]. Asian equations will be used.~~

Section 7.4.5. Pregnancy

Original text

Details of all pregnancies in female subjects will be collected after the start of dosing and until 4 months post-last dose.

Amendment text:

Details of all pregnancies in female subjects will be collected after the start of dosing and until 4 ~~months~~***weeks*** post-last dose.

Section 11. Refences

Original text

Hankinson JL, Kawut SM, Shahar E, Smith LJ, MD, Hinckley Stukovsky K, and Barr RG. Performance of American Thoracic Societh-Recommended Spirometry Reference Values in a Multiethnic Sample of Adults: The Multi-ethnic Study of Antherosclerosis(MESA) Lung Study. *Chest.* 2010;137:138-45.

Amendment text:

~~Hankinson JL, Kawut SM, Shahar E, Smith LJ, MD, Hinckley Stukovsky K, and Barr RG. Performance of American Thoracic Societh-Recommended Spirometry Reference Values in a Multiethnic Sample of Adults: The Multi-ethnic Study of Antherosclerosis(MESA) Lung Study. *Chest.* 2010;137:138-45.~~

Quanjer P, Stanojevic S, Cole T, Baur X., Hall G, Enright P, et al. on behalf of the ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. Eur Respir J. 2012; 40:1324–1343.

.

Section 12.1 Appendix 1- Abbreviations and Trademarks

Original text

N/A	Not applicable
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart Lung and Blood Institute

Amendment text:

N/A	Not applicable
~~NHANES~~	~~National Health and Nutrition Examination Survey~~
NHLBI	National Heart Lung and Blood Institute

12.10.3. Protocol Amendment 3

This amendment applies to all sites participating in Study 201536.

Rationale

This protocol amendment is being implemented to update Secondary Medical Monitor Name and Contact information, clarify eDiary objective assessment links to clinically significant exacerbation and update the wordings about the blinded evaluation of exacerbation.

The following revisions were made:

- Secondary Medical Monitor Name and Contact Information updated
- eDiary objective assessment liks to clinically significant exacerbation clarified

- The wordings about the blinded evaluation of exacerbation updated

List of Specific Changes

Section: Medical Monitor Name and Contact Information

Original text:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	Tel: PPD PPD	PPD	PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China
Secondary Medical Monitor	PPD	PPD	PPD	PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China
SAE		PPD		PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China

Amendment text:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	Tel: PPD PPD	PPD	PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China

Secondary Medical Monitor	PPD	Tel: PPD PPD PPD	PPD	PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China
SAE		PPD		PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China

Section: 7.2. Efficacy Assessment

Original text

Primary Efficacy Endpoint

……

In order to provide an objective assessment of the circumstances linked to the clinical decision that defines asthma exacerbations, the investigator must take into account changes on one or more of the following parameters recorded in the subject's eDiary:

- Decrease in morning PEF ≥30% on at least two of three successive days, compared with baseline (last 7 days of run-in).
- An increase of ≥50% in rescue medication on at least two of three successive days, compared with the average use for the previous week.
- Awakening due to asthma symptoms requiring rescue medication use for at least two of three successive nights.
- A symptom score of 5 for at least two of three successive days

The real-time notification of increasing respiratory parameters from the ediary will triggering contact with the investigator for review via email contact or at a clinic visit.

Amendment text:

Primary Efficacy Endpoint

……

In order to provide an objective assessment of the circumstances linked to the clinical decision that defines asthma exacerbations, the investigator must take into account changes on one or more of the following parameters recorded in the subject's eDiary:

- ~~Decrease in morning PEF ≥30% on at least two of three successive days, compared with baseline (last 7 days of run-in).~~

- ***Decrease in morning peak flow***
- ~~An increase of ≥50% in rescue medication on at least two of three successive days, compared with the average use for the previous week.~~
- ***Increase in the use of rescue medication***
- ~~Awakening due to asthma symptoms requiring rescue medication use for at least two of three successive nights.~~
- ***Increase in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use***
- ~~A symptom score of 5 for at least two of three successive days~~
- ***Increase in overall asthma symptom score***

~~The real-time notification of increasing respiratory parameters from the ediary will triggering contact with the investigator for review via email contact or at a clinic visit.~~

Section 9.2.3 Sample Size Re-estimation or Adjustment

Original text:

Blinded evaluation of exacerbation rates is planned for this study. A blinded evaluation of exacerbation rates for the purpose of sample size re-estimation will be done after one year of enrolment, or when 150 subjects have been randomized, whichever is earlier. A subsequent evaluation will be done after approximately 15 months of enrolment, or when 225 subjects have been randomized, whichever is earlier. If the exacerbation rates for the study are lower than planned, a sample size re-estimation may be conducted. Any subsequent change to the planned number of subjects randomized would be documented in a protocol amendment.

Amendment text:

Blinded evaluation of exacerbation rates is planned for this study. A blinded evaluation of exacerbation rates for the purpose of sample size re-estimation will be done ~~after one year~~

~~of enrolment, or when 150 subjects have been randomized, whichever is earlier. A subsequent evaluation will be done~~ after ~~approximately~~ after15 months of enrolment, or when 225 subjects have been randomized, whichever is earlier. If the exacerbation rates for the study are lower than planned, a sample size re-estimation may be conducted. Any subsequent change to the planned number of subjects randomized would be documented in a protocol amendment.

12.10.4. Protocol Amendment 4

This amendment applies to all sites participating in Study 201536.

Rationale

This protocol amendment is being implemented to update Medical Monitor Name and Contact information, clarify type of exacerbation in some other endpoints related to Systemic corticosteroids (SCS) usage and unscheduled healthcare resource utilization, added "mean days of work/school missed" as an other endpoint, updated analysis in synopsis,updated the study day of V2-1 and V2-2 in Schedule of Activities table, updated time period for collecting SAE information, added population PK analysis as an optional approach for mepolizumab concentration data analysis. Due to the impact of pandemic and observed lower event rates under blind assessment, updated statistical consideration section and change analysis methods to borrow data from MEA115588., and added a statistical appendix.

The following revisions were made:

- Medical Monitor Name and Contact Information updated
- Clarify type of exacerbation in some other endpoints related to SCS usage and unscheduled healthcare resource utilization, add an other endpoint "mean days of work/school missed" which is already included in Health Outcomes section
- Updated Study Day of V2-1 (from day 7 to day 8) and V2-2 (from day 14 to day15) to clarify the duration of PK sample collection, and added a description in SoA Note 3.
- Time period for collecting SAE Information has been updated due to the China local GCP update in 2020. The mentioned SAE reporting collection period will follow China GCP requirement.
- Add population PK analysis as an optional approach for mepolizumab concentration data analysis

- The statistical analyses in synopsis and statistical consideration section have been updated due to a high false negative rate based on the observations during the blinded evaluation if ignore the impact from COVID

List of Specific Changes

Section: Medical Monitor Name and Contact Information

Original text:

Medical Monitor Name and Contact Information

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	Tel: PPD PPD	PPD	PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China
Secondary Medical Monitor	PPD	Tel: PPD PPD	PPD	PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China
SAE		PPD		PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China

Amendment text:

Medical Monitor Name and Contact Information will be provided separately OR can be found in the Study Reference Manual.

~~**Role**~~	~~Name~~	~~Day Time Phone Number and email address~~	~~After-hours Phone/Cell/ Pager Number~~	~~Fax Number~~	~~Site Address~~
~~Primary Medical Monitor~~	PPD	~~Tel:~~ PPD PPD	PPD	PPD	~~Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China~~

~~Secondary Medical Monitor~~	PPD	~~Tel:~~ PPD PPD	PPD	PPD	~~Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China~~
~~SAE~~		PPD		PPD	~~Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China~~

Role	Name	email address	Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	PPD	PPD	PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China
Secondary Medical Monitor	PPD	PPD	PPD	PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China
SAE		PPD		PPD	Building 18, 999 Huanke Road, Pudong, Shanghai, 201203, China

Section 1.1. Synopsis

Original text:

Objectives and Endpoints:

Others	
• To evaluate the effects of mepolizumab compared with placebo on asthma control.	11. Mean number of days with oral corticosteroids taken for exacerbations 12. Total prednisone (or equivalent) exposure for exacerbation over the 52-week treatment period … 17. Unscheduled healthcare resource utilization (for severe exacerbations and other asthma related health care) over the 52-week treatment period

Amendment text:

Objectives and Endpoints:

Others	
• To evaluate the effects of mepolizumab compared with placebo on asthma control.	11. Mean number of days with oral corticosteroids taken for clinically significant exacerbations 12. Total prednisone (or equivalent) exposure for clinically significant exacerbation over the 52-week treatment period … 17. Unscheduled healthcare resource utilization (for clinically significant ~~severe~~ exacerbations and other asthma related health care) over the 52-week treatment period 18. Mean days of School/Work missed over the 52-week treatment period

Section 1.1. Synopsis

Original text:

(no wordings about estimand)

Amendment text:

The primary clinical question of interest is: What is the effect of adding mepolizumab to standard of care when compared with placebo plus standard of care on the rate of exacerbations over 52 weeks in Chinese participants with severe eosinophilic asthma? This question is to be addressed in the absence of study treatment discontinuation.

The estimand is described by the following attributes:

- Population: Chinese participants with severe eosinophilic asthma.
- Treatment condition: mepolizumab 100mg SC given every 4 weeks compared to placebo every 4 weeks, both treatments given on top of standard of care. Further details on standard of care can be found in Section 6.
- Variable: number of clinically significant exacerbations over 52 weeks.
- Summary measure: : annulised rate of exacerbations. Comparison between the mepolizumab arm and placebo will be assessd with the rate ratio.
- Intercurrent events:
  - Study treatment discontinuation-hypothetical strategy
- Rationale for estimand:
  Interest lies in the treatment effect when medication is taken as directed. For participants discontinuing randomised medication, use of a hypothetical strategy addresses treatment effects attributable to mepolizumab in the hypothetical scenario where participants would not discontinue from treatment.

Section 1.1. Synopsis

Original text:

The study is designed to test the superiority of mepolizumab 100 mg SC vs. placebo. Significance tests will be performed at the two-sided 5% alpha level (one-sided 2.5%).

Adjustment for multiplicity will be performed based on the hierarchical testing of the primary and secondary endpoints in a pre-defined order. The primary endpoint will be tested first and if this is significant at the two-sided 5% level, the first of the secondary endpoints will be tested. Hierarchical testing will continue in a similar manner for the remaining secondary endpoints.

The primary and secondary endpoints are defined in the Objective(s)/Endpoint(s) above.

The primary analyses will be performed using a generalized linear model (GLM) assuming the negative binomial distribution. The primary analyses will be based on a two-sided hypothesis testing approach and will use data for the MITT population collected from the start of treatment until the Week 52 visit approximately 4 weeks after the last dose of study medication.

Amendment text:

~~The study is designed to test the superiority of mepolizumab 100 mg SC vs. placebo. Significance tests will be performed at the two-sided 5% alpha level (one-sided 2.5%).~~

~~Adjustment for multiplicity will be performed based on the hierarchical testing of the primary and secondary endpoints in a pre-defined order. The primary endpoint will be tested first and if this is significant at the two-sided 5% level, the first of the secondary endpoints will be tested. Hierarchical testing will continue in a similar manner for the remaining secondary endpoints.~~

~~The primary and secondary endpoints are defined in the Objective(s)/Endpoint(s) above.~~

~~The primary analyses will be performed using a generalized linear model (GLM) assuming the negative binomial distribution. The primary analyses will be based on a two-sided hypothesis testing approach and will use data for the MITT population collected from the start of treatment until the Week 52 visit approximately 4 weeks after the last dose of study medication.~~

The study is designed to determine the effect of Mepolizumab 100mg SC on clinically significant exacerbation events, compared with placebo among Chinese subjects.

The study design mirrors the design of study MEA115588, which demonstrated benefits of mepolizumab compared to placebo for a global population of severe asthma patients with eosinophilic inflammation. This study will evaluate the effects in Chinese patients and, assuming that effects consistent with the global population are observed, a more precise evaluation of the benefit in Chinese patients will conducted by combining data from the local China study with MEA115588 using Bayesian dynamic borrowing (see Statistical Considerations in Section 9). The potential to borrow information from the global dataset is based on the premise that the underlying disease, its general management and the response to mepolizumab is similar in Chinse and non-Chinese patients.

The posterior distributions of the primary endpoint, i.e. rate ratio of events between Mepolizumab 100mg SC vs. placebo will be derived. The hypothesis of interest for treatment comparison is that the rate ratio is less than 1 (alternative hypothesis testing boundary in study MEA115588), and the study will be considered to have shown evidence that supports this hypothesis if the posterior probability that the rate ratio is less than 1 is at least 95% (a “positive result”). Rationales to support this testing criteria can be found in section 9.4.1 (Efficacy Analyses).

The primary analyses will be performed using a generalized linear model (GLM) assuming the negative binomial distribution. The estimate of the rate ratio for mepolizumab vs. placebo as well as an estimate of the dispersion will be provided, they will be combined with global MEA115588 study using the robust mixture prior to obtain the final posterior distribution for the China rate ratio. The mean, median and 90% credible interval of this posterior distribution of the rate ratio will be reported, along with the probability that true rate ratio is less than 1.

The secondary endpoints are defined in the Objective(s)/Endpoint(s) above. No multiplicity adjustment are planned for secondary endpoints.

Section 1.2. Schedule of Activities (SoA)

Original text:

Table 10 Schedule of Activities Table

Procedures	**Pre-screening**	**Screen/Run-in**	**Randomised Treatment (visit window is ± 7 days for V3-V15-2; V2-1, V2-2, V14-1, V14-2 visit window is ± 2 days from V2 or V14 in sub-study)**																		**Exit Visit**			**With-drawal**
Visit	**V0**[1]	**V1**	**V2**[2]	**V2-1**[3]	**V2-2**[3]	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V14-1**[3]	**V14-2**[3]	**V15**	**V15-1**[3]	**V15-2**[3]	**VEW**
Study Week		**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**49**	**50**	**52**	**56**	**60**	
Study Day		**-28~ -7**	**1**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**343**	**350**	**364**	**392**	**420**	
Safety Assessments																								
Adverse Events/Serious Adverse Event Assessment		**X**	X			X	X	X	X	X	X	X	X	X	X	X	X			X			X

3 Only those patients attending the PK sub-study will perform the visit

Amendment text:

Table 11 Schedule of Activities Table

Procedures	Pre-screening	Screen/Run-in	Randomised Treatment (visit window is ± 7 days for V3-V15-2; V2-1, V2-2, V14-1, V14-2 visit window is ± 2 days from V2 or V14 in sub-study)																	Exit Visit			With-drawal
Visit	V0[1]	V1	V2[2]	V2-1[3]	V2-2[3]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V14-1[3]	V14-2[3]	V15	V15-1[3]	V15-2[3]	VEW
Study Week		-4 to -1	0	1	2	4	8	12	16	20	24	28	32	36	40	44	48	49	50	52	56	60	
Study Day		-28~-7	1	~~7~~ 8	~~14~~15	28	56	84	112	140	168	196	224	252	280	308	336	343	350	364	392	420	
Safety Assessments																							
Adverse Events/Serious Adverse Event Assessment			X			X	X	X	X	X	X	X	X	X	X	X	X			X			X

3 Only those patients attending the PK sub-study will perform the visit. Protocol amendment 4 updated Study Day of V2-1 (from day 7 to day 8) and V2-2 (from day 14 to day15) to clarify the duration of PK sample collection. On final PK Sample ID form and related PK CRF forms in InForm System, "VISIT 2 PREDOSE" refers to "VISIT2 DAY1", "VISIT 2 DAY7" refers "VISIT 2 DAY8", and "VISIT 2 DAY 14" refers to "VISIT 2 DAY15" in SoA

Section 3 Objectives and Endpoints

Original text:

Table 2 Study Objectives and Endpoints

Others	
• To evaluate the effects of mepolizumab compared with placebo on asthma control.	11. Mean number of days with oral corticosteroids taken for exacerbations 12. Total prednisone (or equivalent) exposure for exacerbation over the 52-week treatment period 17. Unscheduled healthcare resource utilization (for severe exacerbations and other asthma related health care) over the 52-week treatment period

Amendment text:

Table 2 Study Objectives and Endpoints

Others	
• To evaluate the effects of mepolizumab compared with placebo on asthma control.	11. Mean number of days with oral corticosteroids taken for clinically significant exacerbations 12. Total prednisone (or equivalent) exposure for clinically significant exacerbation over the 52-week treatment period 17. Unscheduled healthcare resource utilization (for ~~severe~~ clinically significant exacerbations and other asthma related health care) over the 52-week treatment period 18. Mean days of School/Work missed over the 52-week treatment period

Section 7.2. Efficacy Endpoints

Original text:

Other Efficacy Endpoints

…

11. Mean number of days with oral corticosteroids taken for exacerbations
12. Total prednisone (or equivalent) exposure for exacerbations over the 52-week treatment period

…

17. Unscheduled healthcare resource utilization (for severe exacerbations and other asthma related health care) over the 52-week treatment period)

Amendment text:

Other Efficacy Endpoints

…

11. Mean number of days with oral corticosteroids taken for clinically significant exacerbations
12. Total prednisone (or equivalent) exposure for clinically significant exacerbations over the 52-week treatment period

…

17. Unscheduled healthcare resource utilization (for ~~severe~~ clinically significant exacerbations and other asthma related health care) over the 52-week treatment period)
18. Mean days of School/Work missed over the 52-week treatment period

Section 7.4.1. Time Period and Frequency for Collecting AE and SAE Information

Original text:

- Any SAEs will be collected from the signing of the informed consent form until at the time points specified in the Schedule of Activities Table.

Amendment text:

- Any SAEs will be collected from ~~the signing of the informed consent form~~ the start of intervention until at the time points specified in the Schedule of Activities Table (Section 1.2).

Section 7.7.1. Health Outcome Endpoints

Original text:

- Mean days of school/work missed

Unscheduled healthcare resource utilization (for severe exacerbations and other asthma related health care)

Amendment text:

- Mean days of school/work missed

Unscheduled healthcare resource utilization (for ~~severe~~ clinically significant exacerbations and other asthma related health care)

Section 9.1 Statistical Hypotheses

Original text:

This study is designed to test the superiority of mepolizumab 100 mg SC vs placebo. Significance tests will be performed at the two-sided 5% alpha level (one-sided 2.5%). A hierarchical testing procedure will be used to provide strong control of type I error for multiplicity across the primary and secondary endpoints.

Amendment text:

~~This study is designed to test the superiority of mepolizumab 100 mg SC vs placebo. Significance tests will be performed at the two-sided 5% alpha level (one-sided 2.5%). A hierarchical testing procedure will be used to provide strong control of type I error for multiplicity across the primary and secondary endpoints.~~

This is a bridging study designed to determine the effect of Mepolizumab 100mg SC on clinically significant exacerbation events, compared with placebo among Chinese subjects.

The Chinese patient data collected in this study will be supplemented with data on the treatment effect for the same exacerbation endpoint from the global PhIII study MEA115588, using a Bayesian Dynamic Borrowing approach to analysis of the study (Schmidli, 2014). The potential to borrow information from the global dataset is based on the premise that the underlying disease, its general management and the response to mepolizumab is similar in Chinese and non-Chinese patients. A bridging approach is proposed because of the expected similarity of the treatment effect in Chinese patients and the global population (supported by similarities in the epidemiology, pathophysiology, pharmacology and clinical management of patients and consistency of treatment differences across key demographic factors including ethnicity), and similar study design specially the study population (supported by similarities in key eligibility criteria) between MEA115588 and this China study, hence there is low probability of the null effect being true.

A frequentist hypothesis test will not be performed. Instead, the posterior distributions of the primary endpoint, i.e. rate ratio of events between Mepolizumab 100mg SC vs. placebo will be derived based on the Bayesian analysis including the global PhIII study MEA115588 information and the data collected on Chinese patients in this study. The hypothesis of interest for treatment comparison is that the rate ratio is less than 1, and the study will be considered to have shown evidence that supports this hypothesis if the posterior probability that the rate ratio is less than 1 is at least 95% (a “positive result”). Please see the Appendix 9 for further information on the choice of posterior probability.

Section 9.2.1 Sample Size Assumptions

Original text:

The primary analysis is based on comparing the rate of clinically significant exacerbations of asthma in subjects treated with mepolizumab 100mg SC vs. Placebo.

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

H_0: $\mu_i = \mu_p$

where μ_i is the rate of clinically significant exacerbations on the mepolizumab 100 mg SC and μ_p is the rate of clinically significant exacerbations on the placebo arm.

The (one-sided) alternative hypothesis is that the rate of clinically significant exacerbations is lower on the mepolizumab arm:

H_a: $\mu_i < \mu_p$

The estimated rate of clinically significant exacerbations in the placebo arm is 1.7 exacerbations per annum (p.a.).

With a two-sided 5% level of significance and a sample size of 256 subjects randomized in a 1:1 ratio (128 subjects in the mepolizumab 100 mg SC treatment group and 128

subjects in the placebo treatment group), it is estimated that the null hypothesis will be rejected if the observed reduction in clinically significant exacerbations for the comparison is at least 26%. Based on a true population reduction of 40% for 100mg SC vs. placebo, there is a 90% chance that the observed reductions will be at least 26 % for the comparison and hence 90% power for demonstrating a statistically significant result for this assumed true population effect.

To account for the loss of patient years data from subjects who withdraw from study treatment early, additional 44 subjects (22 in the mepolizumab treatment arm and 22 in the placebo treatment arm) will be randomized; this approximates to an additional 15% of patients years of data being collected. In total 300 subjects will be randomized into the study with a 1:1 randomization ratio (150 subjects in the mepolizumab 100mg SC treatment group and 150 subjects in the placebo treatment group).

The 40% reduction in exacerbation rate has been selected as reductions of this magnitude or greater have been seen in previous mepolizumab studies MEA112997 and MEA115588. However it should be noted that a smaller reduction in exacerbations could be clinically significant. The estimate of 1.7 exacerbations p.a. for placebo and the estimate of 0.8 for the dispersion parameter are based on the observed data from study MEA115588. This sample size calculation assumes the number of exacerbations per annum (p.a.) follow a negative binomial distribution [Keene, 2007; Zhu, 2014] . For subjects who complete the study, exacerbations occurring on-treatment and within 4 weeks of the last dose will be included in the primary analysis.

Amendment text:

~~The primary analysis is based on comparing the rate of clinically significant exacerbations of asthma in subjects treated with mepolizumab 100mg SC vs. Placebo.~~

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

~~$H_0: \mu_i = \mu_p$~~

~~where μ_i is the rate of clinically significant exacerbations on the mepolizumab 100 mg SC and μ_p is the rate of clinically significant exacerbations on the placebo arm.~~

~~The (one-sided) alternative hypothesis is that the rate of clinically significant exacerbations is lower on the mepolizumab arm:~~

~~$H_a: \mu_i < \mu_p$~~

~~The estimated rate of clinically significant exacerbations in the placebo arm is 1.7 exacerbations per annum (p.a.).~~

~~With a two-sided 5% level of significance and a sample size of 256 subjects randomized in a 1:1 ratio (128 subjects in the mepolizumab 100 mg SC treatment group and 128 subjects in the placebo treatment group), it is estimated that the null hypothesis will be~~

~~rejected if the observed reduction in clinically significant exacerbations for the comparison is at least 26%. Based on a true population reduction of 40% for 100mg SC vs. placebo, there is a 90% chance that the observed reductions will be at least 26 % for the comparison and hence 90% power for demonstrating a statistically significant result for this assumed true population effect.~~

~~To account for the loss of patient years data from subjects who withdraw from study treatment early, additional 44 subjects (22 in the mepolizumab treatment arm and 22 in the placebo treatment arm) will be randomized; this approximates to an additional 15% of patients years of data being collected. In total 300 subjects will be randomized into the study with a 1:1 randomization ratio (150 subjects in the mepolizumab 100mg SC treatment group and 150 subjects in the placebo treatment group).~~

~~The 40% reduction in exacerbation rate has been selected as reductions of this magnitude or greater have been seen in previous mepolizumab studies MEA112997 and MEA115588. However it should be noted that a smaller reduction in exacerbations could be clinically significant. The estimate of 1.7 exacerbations p.a. for placebo and the estimate of 0.8 for the dispersion parameter are based on the observed data from study MEA115588. This sample size calculation assumes the number of exacerbations per annum (p.a.) follow a negative binomial distribution [Keene, 2007; Zhu, 2014] . For subjects who complete the study, exacerbations occurring on-treatment and within 4 weeks of the last dose will be included in the primary analysis.~~

The sample size of 300 participants (considering 256 evaluable participants and additional 44 subjects for drop-out) in a 1:1 ratio has been determined by the superiority testing of mepolizumab 100 mg SC vs. placebo, there will be 90% power to detect a 40% decrease in the exacerbation rate from 1.7 per annum (p.a.) on placebo to 1.02 p.a. on mepolizumab 100mg SC using a two sided 5% significance level. The calculation assumes the number of exacerbations per year follows a negative binomial distribution [Keene, 2007] with a dispersion parameter k=0.8.

During the blinded evaluation, the clinically significant exacerbations which had occurred during the treatment period were analyzed using a generalized linear model assuming a negative binomial distribution and covariates of baseline maintenance OCS therapy (OCS vs. no OCS), EOS level at screening (>=300 cells/μL vs. <300 cells/μL), number of exacerbations in previous year (as an ordinal variable) and baseline disease severity (as % predicted FEV1). The blinded evaluation estimated, the overall event rate based on an assessment of blinded data was observed as 0.78 p.a., the dispersion was 2.0. This was lower than the expected overall event rate of the original study design assumptions.

This observed reduction for overall events at blinded evaluation can be explained by a reduction in exacerbation events during the COVID-19 pandemic, which was not unique in China. , it is still expected that the treatment effect of Mepolizumab compared with placebo will be the same in Chinese SEA population as the original study design assumption. Therefore, according the formula [Friede, 2010]

$$\bar{\lambda} = (\lambda_T + \lambda_P)/2$$

where $\bar{\lambda}$ is the observed overall events rate based on an assement of blinded data, the λ_T and λ_P are the event rates in the treatment and placebo groups, and assuming the reduction in exacerbation rate with Mepolizumab will remain 40% under pandemic, the estimated event rates λ_T and λ_P for Mepolizumab 100mg SC and placebo are 0.975 and 0.585 p.a. respectively. On the other hand, there exists a difference for the estimate of dispersion when data is blinded or unblinded, so that the blinded dispersion estimate is adjusted by the difference between blinded and unblinded, which is 1.6=2.0 *(0.796 / 0.972), where the dispersion in MEA115588 study were 0.796 (unblinded) vs. 0.972 (blinded).

Therefore, based on the conclusion of the blinded evaluation, assuming a 40% decrease in the exacerbation rate from 0.975 per annum (p.a.) on placebo to 0.585 p.a. on mepolizumab 100mg SC will lead to a power of 66% implying a high false negative rate of 34% in China study. If there is a true reduction of 40% in exacerbation rate in Chinese patients, based on use of Bayesian dynamic borrowing with an initial weight of 0.5 on global MEA115588 study result, there will be 88.6% probability to achieve a positive result (equivalent to the power of the study).

The 40% reduction in exacerbation rate has been selected as reductions of this magnitude or greater have been seen in previous mepolizumab studies MEA112997 and MEA115588. However, it should be noted that a smaller reduction in exacerbations could be clinically significant. Under the same assumptions, there will be 99% probability of showing consistent trend, which is defined as the point estimation of rate ratio between Mepolizumab and placebo<1 in China study, with global MEA115588.

Section 9.2.2 Sample Size Sensitivity

Original text:

The sample size in Section 9.2.1 is based on assumed exacerbation rates in the placebo group and an expected reduction in this rate for subjects treated with mepolizumab. If the assumed placebo exacerbation rate or the expected reduction with mepolizumab differ then, at the given sample size there will be an effect on the power of the study. Table 7 illustrates this effect on power of varying placebo rates and reductions in rates with mepolizumab, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals from study treatment, and a dispersion parameter k=0.8.

Table 12 Effect on power of varying placebo rates and reductions in rates with mepolizumab

	Placebo: Exacerbations rate p.a.			
% reduction in exacerbation rate p.a. with mepolizumab	1.0	1.5	**1.7**	2.4
35%	66%	76%	79%	84%
40%	79%	88%	**90%**	93%
45%	89%	95%	96%	98%

The sample size in Section 9.2.1 is based on assumed dispersion parameter of 0.8. If the actual dispersion parameter observed in the study is different, then the power to detect the planned difference in exacerbation rates will be affected.

Table 8 illustrates the estimated power which would be obtained with different dispersion parameter, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals from study treatment, and the placebo and mepolizumab rates are 1.7 and 1.02 respectively. It also shows the estimated sample size which would be required for 90% power.

Table 13 Effect on the power of varying dispersion parameter and sample size required 90% power

Dispersion parameter, k	**Power**	**n per arm required for 90% power (Mepo vs placebo)***
0.7	91%	120 vs. 120
0.8	**90%**	**128 vs. 128**
0.9	88%	136 vs. 136
1.0	86%	144 vs. 144

* Early withdrawal from study treatment is not taken into account.

Amendment text:

~~The sample size in Section 9.2.1 is based on assumed exacerbation rates in the placebo group and an expected reduction in this rate for subjects treated with mepolizumab. If the assumed placebo exacerbation rate or the expected reduction with mepolizumab differ then, at the given sample size there will be an effect on the power of the study. Table 7 illustrates this effect on power of varying placebo rates and reductions in rates with mepolizumab, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals from study treatment, and a dispersion parameter k=0.8.~~

~~Table 14 Effect on power of varying placebo rates and reductions in rates with mepolizumab~~

	~~Placebo: Exacerbations rate p.a.~~			
~~% reduction in exacerbation rate p.a. with mepolizumab~~	~~1.0~~	~~1.5~~	~~**1.7**~~	~~2.4~~
~~35%~~	~~66%~~	~~76%~~	~~79%~~	~~84%~~
~~**40%**~~	~~79%~~	~~88%~~	~~**90%**~~	~~93%~~
~~45%~~	~~89%~~	~~95%~~	~~96%~~	~~98%~~

~~The sample size in Section 9.2.1 is based on assumed dispersion parameter of 0.8. If the actual dispersion parameter observed in the study is different, then the power to detect the planned difference in exacerbation rates will be affected.~~

~~Table 8 illustrates the estimated power which would be obtained with different dispersion parameter, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals from study treatment, and the placebo and mepolizumab rates are 1.7 and 1.02 respectively. It also shows the estimated sample size which would be required for 90% power.~~

~~Table 15 Effect on the power of varying dispersion parameter and sample size required 90% power~~

~~Dispersion parameter, k~~	**~~Power~~**	**~~n per arm required for 90% power (Mepo vs placebo)*~~**
~~0.7~~	~~91%~~	~~120 vs. 120~~
~~0.8~~	**~~90%~~**	**~~128 vs. 128~~**
~~0.9~~	~~88%~~	~~136 vs. 136~~
~~1.0~~	~~86%~~	~~144 vs. 144~~

~~* Early withdrawal from study treatment is not taken into account.~~

The sample size in Section 9.2.1 is based on an expected reduction in this rate for subjects treated with mepolizumab. If the expected reduction with mepolizumab differ then, at the given sample size there will be an effect on the probability of success of the study. Table 7 illustrates this effect on probability of success of varying reductions in rates with mepolizumab, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals from study treatment.

Table 7 Probability of meeting the success criterion conditional on various assumed true treatment effects

Reduction	45%	40%	35%	0
Probabilities of Success	94.6%	88.6%	80.0%	11.8%*

* The false positive rate is calculated as assumed true treatment effects is 0 between Mepolizumab and placebo.

In the Table 7, the probabilities of meeting success are conducted under various assumed trure treatment effects when overall event rate is fixed as 0.78 based on the blinded evaluation and dispersion is 1.6, e.g. when reduction is 40%, then the probability of success is calculated by the exacerbation rates for Mepolizumab 100mg SC and placebo as 0.975 and 0.585 p.a. respectively. Type I error is 11.8%, which is calculated when the

event rate for each group is 0.78, adjusted dispersion is 1.6 based on analyses of blinded evaluation.

Section 9.2.3 Sample Size Re-estimation or Adjustment

Original text:

Blinded evaluation of exacerbation rates is planned for this study. A blinded evaluation of exacerbation rates for the purpose of sample size re-estimation will be done after 15 months of enrolment, or when 225 subjects have been randomized, whichever is earlier. If the exacerbation rates for the study are lower than planned, a sample size re-estimation may be conducted. Any subsequent change to the planned number of subjects randomized would be documented in a protocol amendment.

Amendment text:

Blinded evaluation of exacerbation rates is planned for this study. A blinded evaluation of exacerbation rates for the purpose of sample size re-estimation will be done after 15 months of enrolment, or when 225 subjects have been randomized, whichever is earlier. If the exacerbation rates for the study are lower than planned, a sample size re-estimation may be conducted. Any subsequent change to the planned number of subjects randomized would be documented in a protocol amendment.

By the time of this protocol amendment, blinded evaluations of exacerbation rate were completed indicating the data deviate substantially from the assumptions made when we planned the trial, before the COVID-19 pandemic, thus supporting a protocol amendment to update the planned primary analyses without further adjustment of planned sample size.

Section 9.4 Key Elements of Analysis Plan

Original text:

The primary treatment comparison of interest in this study is mepolizumab 100mg SC vs placebo. This treatment comparison will be made for the primary and secondary endpoints. For each endpoint, different estimands may be explored depending on the scientific question of interest. These will be detailed in the RAP.

Adjustment for multiplicity will be based on hierarchical testing of the primary and secondary endpoints in a pre-defined order. This adjustment will provide strong control of the Type I error. The primary endpoint will be tested first and if this is significant at the two-sided 5% level, the first secondary endpoint will be tested. Hierarchical testing will continue in a similar manner for the remaining secondary endpoints in the following pre-defined order.

- Time to first clinically significant exacerbations.
- Mean change in St. George’s Respiratory Questionnaire at week 52.

- Frequency of exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits over the 52-week treatment period
- Frequency of exacerbations requiring hospitalization over the 52-week treatment period
- Mean change from baseline in clinic pre-bronchodilator FEV1 at Week 52

The primary analyses of efficacy will be performed on the MITT population. The primary endpoint will also be analysed for the PP population.

Amendment text:

~~The primary treatment comparison of interest in this study is mepolizumab 100mg SC vs placebo. This treatment comparison will be made for the primary and secondary endpoints. For each endpoint, different estimands may be explored depending on the scientific question of interest. These will be detailed in the RAP.~~

~~Adjustment for multiplicity will be based on hierarchical testing of the primary and secondary endpoints in a pre-defined order. This adjustment will provide strong control of the Type I error. The primary endpoint will be tested first and if this is significant at the two-sided 5% level, the first secondary endpoint will be tested. Hierarchical testing will continue in a similar manner for the remaining secondary endpoints in the following pre-defined order.~~

- ~~Time to first clinically significant exacerbations.~~
- ~~Mean change in St. George's Respiratory Questionnaire at week 52.~~
- ~~Frequency of exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits over the 52-week treatment period~~
- ~~Frequency of exacerbations requiring hospitalization over the 52-week treatment period~~
- ~~Mean change from baseline in clinic pre-bronchodilator FEV1 at Week 52~~

~~The primary analyses of efficacy will be performed on the MITT population. The primary endpoint will also be analysed for the PP population.~~

The primary treatment comparison of interest in the study is mepolizumab 100mg SC vs placebo. This treatment comparison will be made for the primary and secondary endpoints. There is no adjustment for multiplicity for the secondary endpoints.

Section 9.4.1 Efficacy Analyses

Original text:

(No context before section 9.4.1.1 primary analyses)

Amendment text:

Bayesian Dynamic Borrowing Design

Bayesian dynamic borrowing (BDB) provides a clinically and statistically rigorous method to analyze this China bridging study. An explicit, pre-specified belief about the relevance of the global MEA115588 results to the Chinese population on treatment effect is provided as part of the prior distribution, which is a mixture with two components, one reflecting results from MEA115588 study and a vague component reflecting 'no effect'.

The prior mixture will be upated with the China data to obtain the posterior distribution, which will also be a mixture. The posterior weight given to the global MEA115588 study data is commensurate with the strength of evidence of similarity between the MEA115588 data and the China data. The BDB analysis 'learns' how much of the global MEA115588 study information to borrow based on the consistency between the observed rate ratio in the China and global studies and updates the weight on the global MEA115588 results accordingly.

- The stronger the evidence of consistency, the greater the increase in the updated (posterior) weight on the informative component relative to the prior weight, and hence the greater the borrowing from the global study results.
- Conversely, if the China study results are very different to the global study results, the informative component is down-weighted and final inference is based mostly on the observed data in the China study alone.
- The mechanism by which the weight is updated is entirely pre-specified and mathematically rigorous (Schmidli, 2014)

The informative prior and prior weight in BDB design

The BDB approach will use the results from the global MEA115588 study mixed with a vague component worth two subjectsas an 'informative' but robust prior for the treatment comparison of interest in this China study. There are two primary analysis comparisons: mepolizumab 75mg IV vs placebo and mepolizumab 100mg SC vs placebo for rate of clinically significant exacerbations over the 32 weeks treatment period expressed as exacerbation rate per year in MEA115588. Since the primary outcome, rate of clinically significant exacerbation, showed similar treatment difference in Mepolizumab 75 mg iv group compared with placebo in 32-week Study MEA115588 and 52-week Study MEA112997, this indicates the available efficacy result of Mepolizumab 100 mg SC in 32-week study MEA115588 could also be an informative reference data to bridge to this 52-week China study using the same dose regimen, therefore, the results of mepolizumab 100mg SC vs placebo in study MEA115588 are used to build the global component.

Table 8 The primary analysis of clinically significant exacerbations results in global MEA115588 study

Treatment	No. subjects	Rate ratio (95% CI)	Normal distribution of Rate Ratio (log)	
			Mean	Standard Error
Mepolizumab 100mg SC	194	0.47 (0.35,0.64)	-0.7474	0.1532
Placebo	191			

Source: Table 13 in the CSR of MEA115588.

The logarithmic transformation of the rate ratio will be used, which can be approximately Normally distributed. Therefore, in the primary analysis for the primary treatment comparison of mepolizumab 100mg SC and placebo for the rate of clinically significant exacerbations of asthma over the 52-week treatment period in this study, the global prior component is obtained from the sampling distribution of the log rate ratio between mepolizumab 100mg SC and placebo in the global study MEA115588. The mean log rate ratio and its associated standard error are -0.7474 and 0.1532, respectively, leading to a normal distribution with mean -0.7474 and standard deviation 0.1532 as the global prior component for the primary treatment comparison.

A second vague distribution worth 2 subjects (one in each treatment arm) assuming no treatment effect in China will also be specified, to allow for the possibility that the global MEA115588 data do not provide relevant information about the treatment effect in Chinese patients. A normal distribution with mean zero and standard deviation 2.1256 will be used as vague prior for log rate ratio in BDB design, more details can be found in Appendix 9 Section 12.9.2. A weighted combination of the 'informative' and 'vague' priors will be used to construct a robust mixture prior.

In the primary analysis, a prior weight of 50% is proposed for the informative component of the robust mixture prior, with the remainder of the weight (50%) placed on the vague component to reflect a conservative starting position regarding the assumed relevance of the global MEA115588 results to Chinese patients. See Statistical Appendix 9 Section 12.9.2 for more details on the robust mixture prior and Section 12.9.3 for details on the choice of prior weight.

Effective Sample Size

The updated weight itself is not direactly interpretable as the fraction of the global MEA115588 study sample size that is borrowed. Instead, the effective sample size (ESS) borrowd from the global study can be quantified using the moment method implemented in RBesT R software package version 1.6.1, Table 9 shows the expected value of the ESS borrowed from the global MEA115588 study for each treatment comparison when the true reduction in China is assumed to be 45%, 40%, 35% and 0 as the same with Table 8.

Table 9 Expected Effective Sample Size borrowed per arm from the global MEA115588 study for a range of possible true treatment differences

	The true reduction			
	0	35%	40%	45%
Expected value of ESS borrowed per arm from the global MEA115588 study	-42	76	123	162

Maximum Detectable Value for Rate Ratio

The maximum detectable value (MDV) is the maximum rate ratio that needs to be observed in this China study in order to meet the pre-specified success criteria when combined with the global MEA115588 study results via the Bayesian dynamic borrowing analysis. Under the current sample size of 300 participants in total (256 evaluable participants and 44 subjects for drop out), assuming overall event rate is 0.78 p.a. based on the blinded evaluation and dispersion is 1.6, chosen weight on global component in the mixture prior of 0.5, and success rule that the posterior probability of the true rate ratio in China being less than 1 is at least 95%, the MDV for rate ratio between mepolizumab and placebo is 0.776. That corresponds to a minimum detectable reduction for mepolizumab compared with placebo of at least 22.4%.

Section 9.4.1.1 Primary Analyses

Original text:

The primary treatment effect to be estimated in this study is the frequency of clinically significant exacerbations of asthma over the 52-week treatment period expressed as an exacerbation rate p.a. Exacerbation from the start of treatment until 4 weeks after the last dose of study drug will be used in the analysis. Exacerbations which are separated by less than 7 days will be treated as a continuation of the same exacerbation.

The numbers of clinically significant exacerbations are assumed to follow a negative binomial distribution. The logarithm of time on treatment will be used as an offset variable. The primary analysis of the rate of exacerbations will use a generalised linear model with a log-link function. This model will include covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), EOS level at screening ($\geqslant$300 cells/μL vs. <300 cells/μL), number of exacerbations in previous year (as an ordinal variable), baseline disease severity (as % predicted FEV_1). The adjusted mean rates per year, pair-wise treatment ratios and associated p-values and confidence limits will be presented.

The analysis will be performed on the MITT population. A supporting analysis of the PP population will also be performed.

Alternative estimands may be explored in the RAP.

Amendment text:

~~The primary treatment effect to be estimated in this study is the frequency of clinically significant exacerbations of asthma over the 52-week treatment period expressed as an exacerbation rate p.a. Exacerbation from the start of treatment until 4 weeks after the last dose of study drug will be used in the analysis. Exacerbations which are separated by less than 7 days will be treated as a continuation of the same exacerbation.~~

~~The numbers of clinically significant exacerbations are assumed to follow a negative binomial distribution. The logarithm of time on treatment will be used as an offset variable. The primary analysis of the rate of exacerbations will use a generalised linear model with a log-link function. This model will include covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), EOS level at screening (≥300 cells/μL vs. <300 cells/μL), number of exacerbations in previous year (as an ordinal variable), baseline disease severity (as % predicted FEV_1). The adjusted mean rates per year, pair-wise treatment ratios and associated p-values and confidence limits will be presented.~~

~~The analysis will be performed on the MITT population. A supporting analysis of the PP population will also be performed.~~

~~Alternative estimands may be explored in the RAP.~~

The primary treatment effect to be estimated in this study is the frequency of clinically significant exacerbations of asthma over the 52-week treatment period expressed as an exacerbation rate p.a. Exacerbation from the start of treatment until 4 weeks after the last dose of study drug will be used in the analysis. Exacerbations which are separated by less than 7 days will be treated as a continuation of the same exacerbation.

The numbers of clinically significant exacerbations are assumed to follow a negative binomial distribution. The logarithm of time on treatment will be used as an offset variable. The primary analysis of the rate of exacerbations will use a generalized linear model with a log-link function. This model will include covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), number of exacerbations in previous year (as an ordinal variable), baseline disease severity (as % predicted FEV1). The estimate of the logarithm of the rate ratio for mepolizumab vs. placebo and associated standard error will be the data used to update the robust mixture prior to obtain the final posterior distribution for the China rate ratio (on the log scale).

The mean, median and 90% credible interval of this posterior distribution of the rate ratio will be reported, along with the probability that true rate ratio is less than 1 (equivalent to the log rate ratio being less than 0).

The following 2-component mixture prior will be used for the log rate ratio:

$$p(\theta) = 0.5 * Normal(-0.7474\ , 0.1532) + 0.5 * Normal(0\ 2.1256)$$

Sensitivity analysis will be conducted to assess the impact of different prior weights on the 'informative' component of the robust mixture prior, and the details will be specified in the RAP.

For the intercurrent event of withdrawal from study treatment, hypothetical strategy will be applied for primary analysis, where the logarithm of time on treatment will be used as an offset variable in the model.

The detailed missing data imputation method and supportive analysis will be defined in full RAP.

Section 9.4.1.2 Key Secondary Analyses

Original text:

…

Time to first clinically significant exacerbations will be analysed using Cox's proportional hazards model with covariates of treatment group, baseline maintenance OCS therapy, EOS level at screening, number of exacerbations in previous year (as an ordinal variable), baseline disease severity (as % predicted FEV1).

St. Georges Respiratory Questionnaire (SGRQ) score will be analysed using mixed repeated measures model adjusting for baseline maintenance OCS therapy, baseline SGRQ, EOS level at screening, number of exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, and treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.

The secondary endpoints of rate of exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits and rate of clinically significant exacerbations requiring hospitalization will be analyzed using negative binomial regression, as described for the primary endpoint above.

Pre-bronchodilator FEV1 will be analyzed using mixed effects repeated measures model adjusting for baseline maintenance OCS therapy, EOS level at screening, baseline FEV1, number of exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, and treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group.

Amendment text:

…

Time to first clinically significant exacerbations will be analysed using Cox's proportional hazards model with covariates of treatment group, baseline maintenance OCS therapy, ~~EOS level at screening,~~ number of exacerbations in previous year (as an ordinal variable), baseline disease severity (as % predicted FEV1).

St. Georges Respiratory Questionnaire (SGRQ) score will be analysed using mixed repeated measures model adjusting for baseline maintenance OCS therapy, baseline SGRQ, ~~EOS level at screening,~~ number of exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, and treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.

The secondary endpoints of rate of exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits and rate of clinically significant exacerbations requiring hospitalization will be analyzed using negative binomial regression, as described for the primary endpoint above.

Pre-bronchodilator FEV1 will be analyzed using mixed effects repeated measures model adjusting for baseline maintenance OCS therapy, ~~EOS level at screening,~~ baseline FEV1, number of exacerbations in previous year (as an ordinal variable), ~~baseline % predicted FEV1,~~ and treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group.

The point estimate as well as the estimate of the variability in above analyses will be provided. More details will be provided in full RAP.

Section 9.4.2.4 Other Safety Measures

Original text:

Actual values and change from baseline for other scheduled safety assessments such as vital signs (pulse rate, systolic and diastolic blood pressure), 12-lead ECG parameters (QTcF, QTcB and heart rate) will be summarized at each scheduled visit. Further details will be provided in the RAP.

Amendment text:

Actual values and change from baseline for other scheduled safety assessments such as vital signs (pulse rate, systolic and diastolic blood pressure), 12-lead ECG parameters (QTc ~~QTcF, QTcB~~ and heart rate) will be summarized at each scheduled visit. Further details will be provided in the RAP.

Section 9.4.3. Pharmacokinetic analyses

Original text:

- The mepolizumab plasma concentrations from this study will be analyzed using non-compartmental analysis. If data permits, population PK analysis will be conducted using, for example, NONMEM 7 for determination of the population and/or individual systemic exposure, volume of distribution and clearance as well as characterise the between- and within subject variability.

Amendment text:

- The mepolizumab plasma concentrations from this study will be analyzed using non-compartmental analysis and/or population PK analysis approach. When population PK analysis is considered necessary, it will be conducted using, for example, NONMEM 7 for determination of the population and/or individual systemic exposure, volume of distribution and clearance as well as characterise the between- and within subject variability.

Section 11. Reference

Original text:

…

Zhu Haiyuan, Lakkis Hassan. Sample size calculation for comparing two negative binomial rates. *Statist.Med.* 2014;33(3):376-87.

Amendment text:

…

Zhu Haiyuan, Lakkis Hassan. Sample size calculation for comparing two negative binomial rates. *Statist.Med.* 2014;33(3):376-87.

Friede T, Schmidli H. Blinded sample size reestimation with count data: methods and applications in multiple sclerosis. *Statist.Med.* 2010;29:1145-1156.

Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics.* 2014;70:1023-1032.

Appendix 9

Original text:

Appendix 9: protocol amendment changes

…

Amendment text:

Appendix 9 statistical appendix

12.9.1 Choice of posterior probability

A 95% posterior probability that the true rate ratio < 1 represents a high level of confidence for declaring a positive treatment benefit in Chinese patients in the context of

a bridging study where substantial evidence of treatment benefit in global (non-Chinese) patients already exists and is aligned with examples of Bayesian decision criteria given in the FDA draft guidance on Complex Innovative Designs [https://www.fda.gov/media/130897/download]. This represents a more rigorous evidentiary threshold than is typically provided by a 'positive trend 'design, which requires only that the observed rate ratio < 1.

12.9.2 overview of the proposed robust mixture prior and analysis strategy

In order to formally incorporate the global MEA115588 study data in this study, the Bayesian analysis with a robust mixture prior distribution [Schmidli, 2014], which allows for "dynamic borrowing" of prior information, will be conducted. This analysis learns how much of the global prior information to borrow based on the consistency between the China data and global prior. The mixture prior was constructed by two components.

- Component 1 is an informative prior based on the observed efficacy response from global study MEA115588, referred to as the "global prior"
- Component 2 is a "vague" prior centred on a mean of zero and with variance scaled to represent information equivalent to one subject

Denoting the log rate ratio for Mepolizumab 100mg SC vs. placebo as θ, the prior has the form

$$p(\theta) = w * p_1(\theta) + (1 - w) * p_2(\theta)$$

where $p_1(\theta)$ is the component containing the information from the global study prior, $p_2(\theta)$ is the vague component and w is the weight.

The prior weight w assigned to the informative prior component represents the prior degree of confidence in the extrapolation strategy. At lower prior weight the mixture prior presents a heavier tailed distribution with more prior weight being applied to the non-informative vague prior component. When the mixture prior is combined with the observed global data, w is updated according to how consistent China data are with the global prior: the stronger the evidence of consistency, the greater the increase in the posterior weight w^* relative to the prior weight w. Conversely, when there is prior-data conflict, w^* will be lower than w and will tend to zero as evidence of conflict increases, so that the global information is down-weighted and posterior inference is based almost entirely on the China data.

12.9.2.1 The informative (global) prior

The global prior distribution was constructed using a normal approximation to the sampling distribution of the observed log rate ratio of exacerbations on mepolizumab vs. placebo in the subjects from global study MEA115588. The point estimation and standard error for the log rate ratio obtained from negative binomial regression of the observed exacerbation counts were used as the mean and standard deviation, respectively, of a normal prior distribution for the global efficacy response. Therefore, based on the

results in global MEA115588 presented in Table 8 it provided a Normal $(-0.7474, 0.1532^2)$ as the global prior for log rate ratio.

12.9.2.2 The vague prior

The vague prior has a mean of 0 for rate ratio on log scale (i.e. no effect in China), and the variance is scaled such that the information content of the prior is approximately equivalent to that provided by two subjects, one subject per arm. This variance was determined by taking the squared standard error of the log rate ratio obtained from the global data and multiplying it by N/2, where N is the total MEA115588 sample size. Therefore, the SD of the vague prior is

$$SD = \sqrt{0.1532^2 * \frac{385}{2}} = 2.1256$$

12.9.2.3 Initial weight on informative (global) prior component and mixture prior

An initial (prior) weight of 50% is proposed for the informative global component of the robust mixture prior, with the remainder of the weight (50%) placed on the vague prior to reflect a conservative starting position regarding the assumed relevance of the global MEA115588 results to Chinese. Combining the two components and their respective weights gives the following 2-component mixture normal:

$$p(\theta) = 0.5 * Normal(-0.7474\,, 0.1532) + 0.5 * Normal(0\,, 2.1256)$$

12.9.3 Choice of weights

The scientific grounds for expecting similar benefit: risk profile in China and global study patients justifies a high initial weight on the informative component. However, based on an extensive review of the impact of the prior weight specified for the global MEA115588 study (prior weights explored were: 0, 0.1, 0.2, …0.9,1), a more conservative prior weight of 50% was felt to provide an acceptable trade-off between the risks of a false positive result and a false negative result, and to enable meaningful gains in precision due to borrowing information from the global study whilst ensuring that the prior does not dominate the posterior completely but allows the observed data in Chinese patients to contribute to the inference from the study.

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