TITLE PAGE

Protocol Title: A multi-centre, open-label extension, safety study to describe the long-term clinical experience of mepolizumab in participants with hypereosinophilic syndrome (HES) from Study 200622

Protocol Number: 205203/ 02

Short Title: A multi-centre, open-label extension, safety study of mepolizumab in participants with hypereosinophilic syndrome (HES) from Study 200622

Compound Number: SB240563

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

PPD

16 Nov 2017

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Date

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 02	16-Nov-2017
Amendment 01	13-Jan-2017
Original Protocol	02-Nov-2016

Amendment 02 16-NOV-2017

Overall Rationale for the Amendment: To add the optional biomarker sub-study and update the text around the HES therapy adjustment after HES flare considering therapy reduction during the study.

Section # and Name	**Description of Change**	**Brief Rationale**
2. Schedule of Activities 9.8.2. Biomarker Sub-study	Information about the optional biomarker sub-study and sample collection schedule was added to the protocol.	The optional biomarker sub-study has been added.
9.1.1. HES Flare	The text was updated from "Investigators are encouraged, as medically appropriate, to return the subject's treatment regimen to the baseline (Visit 2) after the flare has resolved." to "Investigators are encouraged, as medically appropriate, to return the subject's treatment regimen to level prior to the flare after the flare has resolved."	The text around HES therapy adjustment after the HES flare has been updated considering that investigators may adjust the participants' background HES therapy per standard of care starting at Visit 2 (approximately 4 weeks after the first dose).
1. Synopsis, 2. Schedule of Activities, 3. Background, 5.1. Overall Design, 7.7. Treatment after the End of the Study	'MHE104317/MHE112562' has been replaced with 'mepolizumab HES expanded access'.	GSK tracking numbers have been replaced with the term, 'mepolizumab HES expanded access' to describe the program.

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1. SYNOPSIS

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Short Title: A multi-centre, open-label extension, safety study of mepolizumab in participants with hypereosinophilic syndrome (HES) from Study 200622

Rationale:

Study 200622 is a 32-week treatment period, randomized, double-blind, placebo-controlled, parallel group, multicentre study of mepolizumab in adolescent and adult participants with severe hypereosinophilic syndrome (HES) receiving standard of care (SoC) therapy. Participants will be randomized in a 1:1 ratio to receive either 300 mg mepolizumab *or* placebo subcutaneously (SC) every 4 weeks while continuing their HES therapy.

The rationale for Study 205203 is to have Study 200622 participants continue 4-weekly dosing with open-label mepolizumab 300mg SC for an additional 20 weeks after completing the 32-week study assessments post-randomization. While the 32-week phase 3 data from Study 200622 will be the basis to demonstrate the clinical benefit of mepolizumab and support the registration of mepolizumab for the indication of HES, combining the data from 205203 and 200622 will provide up to 52-week exposure data to further characterize the long-term safety profile of mepolizumab and provide additional data on the clinical benefit in HES patients beyond 32 weeks.

This study will provide Study 200622 participants who meet the current study eligibility criteria the option of receiving treatment with mepolizumab as an add-on to their SoC treatment for HES post-study.

Objectives and Endpoints:

Objectives	Endpoints
Primary - Safety • To describe the long-term safety profile of mepolizumab in participants with HES who took part in Study 200622.	• Adverse events (AEs) [serious and non-serious] • Anti-drug antibody
Other – Safety • To describe the long-term safety profile of mepolizumab in participants with HES who took part in Study 200622.	• Vital signs • 12-lead ECG • Hematological and clinical laboratory tests

Objectives	Endpoints
Exploratory - Efficacy • To assess the effect of long-term use of mepolizumab on multiple clinical outcomes.	• Rate of HES flare# • Change in the mean daily OCS dose from Weeks 0-4 to Weeks 16-20 • Proportion of participants who achieve a mean daily OCS (prednisone/prednisolone or equivalent) dose of ≤7.5mg during Weeks 16-20
Pharmacodynamic (PD) • To assess the effect of long-term use of mepolizumab on a PD marker	• Blood eosinophil levels

HES flare as defined in Section 9.1.1.

Overall Design:

This is a multi-centre, open-label extension, 20-week treatment period, safety study of mepolizumab in adolescent and adult participants with HES who took part in the phase 3 Study 200622.

Study 200622 participants who meet one of the following criteria will be screened to continue with Study 205203:

i. Completion of the 32-week treatment period in Study 200622,

or

ii. If the participant was withdrawn from study treatment prematurely during the 200622 study, but continued in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization.

Eligible participants will receive 300mg SC mepolizumab every 4 weeks starting approximately 32 weeks after the first dose of study treatment in Study 200622. In this OLE Study 205203, the final dose of mepolizumab will be administered at Visit 5 (Week 16). Assessments during the Visit 6 (20 weeks after first dose and 4 weeks after the last dose) will complete the study treatment period.

During Study 205203, investigators will be blinded to the blood eosinophil count (Section 12.2) for the sample collected at Visit 1 (1st dosing visit), after which blood eosinophil counts will be unblinded starting at Visit 2. Investigators may adjust the participants' background HES therapy per standard of care starting at Visit 2 (approximately 4 weeks after the first dose).

Participants who complete assessments at Visit 6 (Week 20) may continue with mepolizumab treatment via mepolizumab HES expanded access (e.g., MHE104317,

MHE112562), where local regulation permits. Study 205203 participants who do not continue with mepolizumab HES expanded access will have an additional follow-up assessment at Visit 7 (28 weeks after first dose and 12 weeks after the last dose of mepolizumab).

Number of Participants:

Approximately 80 participants will be randomized in the initial recruitment phase for Study 200622. The proportion of participants that have an HES flare will be monitored and the total number of participants randomized may be increased if the blinded overall rate is predicted to be <30%. The sample size may be increased up to a maximum of 120 participants in total. Participants who completed required assessments for 32 weeks starting from randomization in Study 200622 may be evaluated for eligibility to participate in Study 205203.

Treatment Groups and Duration:

All participants will receive 300mg mepolizumab SC every 4 weeks for the duration of 20 weeks.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	**Screening/Baseline**	**20-Week Treatment Period**					**WD (4 weeks post-last dose) ± 1 wk**	**Study Visit 7 Additional follow-up (12 weeks post-last dose ± 1 wk**	**Flare**	**Notes**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**				
Study Weeks	**0**	**4 ± 1 wk**	**8 ± 1 wk**	**12 ± 1 wk**	**16 ± 1 wk**	**20 ± 1 wk**				
Informed consent	X									
Inclusion and exclusion criteria	X									
Demography	X									
Full physical examination including height and weight	X									
Past and current medical conditions	X									
Urine pregnancy test (WOCBP only) – serum test if locally required	X	X	X	X	X	X	X	X		Test is required for WOCBP on study treatment until the last follow-up.
Clinical safety laboratory assessments (include liver chemistries)	1	2	2	2	2	1	1		2	**1**: Hematology, chemistry, aldolase, troponin, urinalysis **2**: Hematology, chemistry, aldolase, troponin
PK	X					X	X	X		
Immunogenicity (Anti-drug antibody)	X					X	X	X		

Procedure	Screening/Baseline	20-Week Treatment Period					WD (4 weeks post-last dose) ± 1 wk	Study Visit 7 Additional follow-up (12 weeks post-last dose ± 1 wk	Flare	Notes
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**				
Study Weeks	**0**	**4 ± 1 wk**	**8 ± 1 wk**	**12 ± 1 wk**	**16 ± 1 wk**	**20 ± 1 wk**				
Sample collection for optional biomarker sub-study	X					X	X		X	Sample collection for the optional biomarker sub-study should be done after obtaining a written consent.
12-lead ECG	X					X	X			
Vital signs	X	X	X	X	X	X	X		X	
HES Core Assessments/HES flare details	X	X	X	X	X	X	X		X	
Study treatment	X	X	X	X	X					
AE review	X	X	X	X	X	X	X	X	X	
SAE review	X	X	X	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	

wk: week

- The baseline visit is the exit visit (32 weeks after randomization) for Study 200622. Assessments that are captured as part of the exit visit for Study 200622 do not have to be repeated. Information will be transferred accordingly.
- Biological sample collection (for clinical safety laboratory, PK, and immunogenicity) is done prior to administration of study treatment on dosing visits (Visits 1 2, 3, 4, 5) as specified in the SoA.
- WD: Prematurely discontinuation of mepolizumab (~4 weeks after the last dose of mepolizumab).
- Visit 7 - Additional follow-up is required 12 weeks after the last dose of mepolizumab for participants who do not continue with mepolizumab via mepolizumab HES expanded access at that time.

- Participants who prematurely discontinue study treatment will attend 4-weekly study visits (e.g., Visit 2, 3, 4, 5) to complete all assessments/procedures as noted in the SoA except for administration of study treatment and pre-dose pregnancy test for women of childbearing potential (WOCBP). For additional assessments at 4 weeks and 12 weeks after the last dose of mepolizumab (duplicate assessments in 4-weekly study visits and 4 weeks/12 weeks post-last dose assessments are completed only once), refer to 'WD' and 'Visit 7- Additional follow-up'.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

3.1. Study Rationale

Study 200622 is a 32-week treatment period, randomized, double-blind, placebo-controlled, parallel group, multicentre study of mepolizumab in adolescent and adult participants with severe hypereosinophilic syndrome (HES) receiving standard of care (SoC) therapy. Participants will be randomized in a 1:1 ratio to receive either 300 mg mepolizumab *or* placebo subcutaneously (SC) every 4 weeks while continuing their HES therapy.

The rationale for Study 205203 is to have Study 200622 participants continue 4-weekly dosing with open-label mepolizumab 300mg SC for an additional 20 weeks after completing the 32-week study assessments post-randomization. While the 32-week phase 3 data from Study 200622 will be the basis to demonstrate the clinical benefit of mepolizumab and support the registration of mepolizumab for the indication of HES, combining the data from 205203 and 200622 will provide up to 52-week exposure data to further characterize the long-term safety profile of mepolizumab and provide additional data on the clinical benefit in HES patients beyond 32 weeks.

This study will provide Study 200622 participants who meet the current study eligibility criteria the option of receiving treatment with mepolizumab as an add-on to their SoC treatment for HES post-study.

3.2. Background

HES is a heterogeneous group of chronic inflammatory disorders characterized by persistent eosinophilia (elevated blood eosinophil counts) and diverse organ involvement, punctuated by flares of disease worsening. Inadequate HES treatment can lead to profound end-organ damage and increased mortality. Given the clinical heterogeneity of HES, clinicians use diverse classes of medications (such as high doses of oral corticosteroids), most of which are not approved to treat HES, have detrimental side effects, and may not result in complete remission of disease.

Mepolizumab is a humanized monoclonal antibody (IgG1, kappa, mAb) which is specific for human IL-5. Mepolizumab blocks binding of human IL-5 (hIL-5) to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. In conditions where eosinophilia is considered to play an important part in the pathology, including severe eosinophilic asthma and Eosinophilic Granulomatosis with Polyangiitis (EGPA), a consistent reduction in blood eosinophil counts is observed in association with mepolizumab administration, with concomitant clinical improvement [Haldar, 2009; Kim, 2010; Moosig, 2011; Nair, 2009; Ortega, 2014; Pavord, 2012]. The potential benefit of mepolizumab in patients with HES has been supported by clinical data from previously completed clinical studies (MHE100185 [Rothenberg, 2008], MHE100901 [Roufosse, 2013], CRT112446 [Stein, 2008]). In addition, the ongoing mepolizumab HES expanded access program (MHE104317 as well as named patient supply [MHE112562 and 112000]) with over 200 patients (interim data cut-off date of 23

September 2013) demonstrated that mepolizumab is well tolerated and provides long-term disease control to some patients with HES [Duncan, 2015].

3.3. 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 (IB).

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) - mepolizumab		
Risk of systemic reactions including allergic reactions	• In the placebo-controlled severe asthma studies both acute and delayed systemic reactions including hypersensitivity have been reported following administration of mepolizumab with incidence rates similar between mepolizumab and placebo-treated participants (6% in the mepolizumab [all doses combined] group and 3% in the mepolizumab [100 mg SC/75 mg IV] combined group as compared with 5% in the placebo group). The most common symptoms reported with any systemic reaction included headache, rash, pruritus, fatigue, and dizziness. • While rare, serious systemic reactions including anaphylaxis have been reported. • Reactions reported to date across the mepolizumab program are summarized in the IB 'Adverse Events of Special Interest' section; see also 'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	• Daily monitoring of serious AEs (SAEs) by GSK Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK study team and/or GSK safety review team. • Customized AE and SAE case report form (CRF) utilized for targeted collection of systemic reactions data. • Utilization of anaphylaxis diagnostic criteria as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Section 12.7). • Participants are monitored in clinic for 1 hour for the 1st three administrations following dosing with mepolizumab, then follow monitoring policies for the center.
Risk of local injection site reactions	• In the placebo-controlled severe asthma studies an increase in the incidence of local injection site reactions has been observed with SC administration of mepolizumab compared with	• Daily monitoring of serious AEs (SAEs) by GSK Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	placebo (8% vs. 3%). There have been no reports of severe reactions. Pain, erythema, swelling, itching, and burning sensation were the most common symptoms reported. • Local injection site reactions reported to date across the mepolizumab program are summarized in the Adverse Events of Special Interest' section of the IB; see also 'Section 6 titled 'Summary of Data and Guidance for the Investigator'.	study team and/or GSK safety review team. • Customized AE and SAE case report form (CRF) will be utilized for targeted collection of systemic reactions data.
Potential risk of immunogenicity	• Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralizing antibodies (NAB), which have the potential to modulate pharmacokinetics (PK), pharmacodynamics (PD) or produce adverse reactions. However, humanized and fully human antibodies are less immunogenic than mouse or chimeric monoclonal antibodies. • In the placebo controlled severe asthma studies low incidence (6% 100 mg SC and 2% all IV doses) and low titer of ADA and neutralizing antibodies have been reported. To date there have been no apparent association with adverse events, loss of disease control and/or markedly altered PK or PD profiles associated with anti-mepolizumab antibodies in any participants. Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; see Section 5.4. 'Clinical Immunogenicity'	To characterize the potential risk of immunogenicity: • Blood samples are collected in clinical studies for detection of both ADA and NAB. • For participants who develop anti-mepolizumab antibodies systematic review of AE/SAE data at the end of the study will be conducted.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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'.	
Potential risk for adverse cardiovascular (CV) effects	• Mepolizumab binding was restricted to human lymphoid tissues in an immunohistochemistry tissue binding study suggesting a low likelihood of non-pharmacologic effects on CV function. • No AEs concerning cardiac conduction or repolarization evident in cynomolgus monkeys at doses at least 10-fold in excess of humans dosed at 10 mg/kg or 750 mg. • No clinically relevant trends observed in electrocardiogram (ECG) data in humans. • In study **MHE100185** HES participants received mepolizumab 750 mg IV every 4 weeks for up to 36 weeks, cardiac events were reported by 7% of participants in both mepolizumab and placebo arm s. There was 1 death, due to cardiac arrest in the mepolizumab group not considered related to mepolizumab treatment. This subject had severe HES with multiple cardiovascular complications and concurrent renal failure. Other cardiac disorder AE occurred is palpitation (2 participants in the mepolizumab group and 1 subject in the placebo group). The following events reported in the placebo arm only: cardiovascular disorder, arterial dilatation, ventricular dysfunction and ventricular	• Daily monitoring of SAEs by GSK Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or GSK safety review team. • CV monitoring for study includes: o Enhanced baseline collection of CV risk factors & functional status; o Baseline evaluation of clinical symptoms of ischemic heart disease, if clinically indicated.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	hypertrophy. • In study **MHE100901** (open-label extension [OLE] study to MHE100185 above), participants received mepolizumab 750 mg IV for up to 67 months, 1 fatal and 2 non-fatal SAEs reported due to cardiac failure, none considered related to mepolizumab. • In study **MHE104317** (compassionate use) 7% of patients reported SAEs of cardiac disorders. 3 SAEs reported, 1 secondary to CHF, 1 due to cardiac arrest, & 1 due to MI, all were considered unrelated to mepolizumab. **Severe Asthma:** • In Study MEA112997, a numeric imbalance in the number of serious cardiac events was observed for mepolizumab (7 participants: 2/153 on 75 mg IV [3 events: myocardial ischemia, acute myocardial infarction, coronary artery thrombosis], 1/152 on 250 mg IV [1 event: coronary artery insufficiency] and 4/156 on 750 mg IV [4 events: myocardial ischemia, atrial fibrillation, myocardial infarction and supraventricular tachycardia]) compared with placebo (1 of 155 participants reported atrial flutter). This imbalance was not replicated in subsequent Phase III placebo-controlled studies, MEA115588 and MEA115575, and it was not observed previously in other controlled asthma trials or in other populations studied	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	such as HES. • In the OLE studies, cardiovascular events were similar in frequency and type with those reported from the placebo-controlled severe asthma (PCSA) studies. Cardiovascular events in the severe asthma program are summarized under AE of special interest (AESI) section of the IB.	
Potential risk of alterations in immune response, potentially leading to increase in infections	• This is a theoretical concern with biologics; however, critical review of preclinical toxicity data and pharmacological properties of mepolizumab suggests that the risk for potential immunotoxicity is low. • No evidence of increased incidence of infections in any preclinical studies. • Murine data demonstrate that IL-5 antagonism is unlikely to influence cellular or humoral immunity, particularly in response to parasitic infections. • No mepolizumab-related effects on lymphocyte immunophenotyping in monkeys or humans, including T-cell activation, distribution of CD4/CD8 subtypes or Th1/Th2 cytokine patterns, B-cells, NK cells or γδ-T-cells. • Across all PCSA, the frequency of participants with infections was similar between placebo (239/412 or 58%), mepolizumab 100 mg SC	• Eosinophils may be involved in the immunological response to some helminth infections. Participants with recent parasitic (helminth) infections will be excluded from the study or required to be adequately treated for helminth infections before initiation of study treatment. If a subject becomes infected whilst receiving study treatment and does not respond to anti-helminth treatment, temporary discontinuation of study treatment should be considered in consultation with GSK Medical Monitor. • Daily monitoring of SAE by GSK Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK study team and/or GSK safety review team

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	(136/263 or 52%) and mepolizumab 75 mg IV (209/344 or 61%). • In the OLE studies, rates of infections, including all infections, serious and opportunistic infections, were similar to those from the PCSA studies • Infections reported to date across the mepolizumab development program are summarized in the IB; see 'Special Precautions and Warnings' (for exclusion of participants with underlying parasitic infections) and 'Undesirable Effects' HES subsection (for very common infections of nasopharyngitis, upper respiratory tract infection (URTI), rhinitis and bronchitis reported in other patient populations) sections located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	
Potential risk of alterations in immune response potentially leading to increase in malignancies	• Non-clinical and clinical experience to date does not support a role for mepolizumab in the development of malignancies. No evidence of defective tumor surveillance in IL-5 or eosinophil-deficient mice. Mepolizumab is not believed to possess an inherent carcinogenic potential or increase the susceptibility to tumor formation secondary to significant immunosuppression, and there is no evidence to date that mepolizumab has produced immunosuppression in animals. • Reports of malignancies in the overall	• Participants with current malignancy or malignancy that developed during Study 200622 will be excluded from the study. Participants who had localized carcinoma (i.e., basal or squamous cell) of the skin which was resected for cure will not be excluded. • Daily monitoring of SAEs by GSK Medical Monitor; regular systematic review of AE/SAE data from this study by GSK study team and/or GSK safety review team

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	mepolizumab program (including asthma, HES, other eosinophil-driven diseases & healthy participants) were similar across treatment groups and are those types common in the general population with a frequency rate of <1% at all individual doses and all doses of mepolizumab combined. A review of a well-established cohort of patients with hyperoesinophilia including those with HES at the Mayo clinic showed that 5.1% developed hematologic malignancy over 13-year period; the median time the malignancy developed was 10 months after the onset of hypereosinophilia. T-cell derived malignancies were most commonly diagnosed [Jin, 2015]. Malignancies, including lymphoma, reported to date across the mepolizumab program (severe asthma and HES) are summarized in the IB; see also 'Special Warnings and Special Precautions for Use' section located in IB Section 6 titled 'Summary of Data and Guidance for the Investigator'.	
Potential risk for exaggerated response of symptoms upon cessation of treatment	• No apparent rebound eosinophilia observed in monkeys treated with mepolizumab. • Across the PCSA program, post-treatment AEs of asthma did not appear to occur at a significantly greater incidence following cessation of treatment with mepolizumab compared with placebo. Clinical data in severe	• Daily monitoring of SAEs by GSK Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or GSK safety review team

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	asthma did not show evidence of symptom rebound after cessation of mepolizumab. Participants enrolled in the OLE study MEA115666 study previously participated in the Phase III PCSA study MEA112997 and had a treatment break of a minimum of 12 months between studies. Of the 347 participants enrolled in MEA115666, 22% received placebo in MEA112997 and 24%, 26%, and 28% received 75 mg, 250 mg, and 750 mg mepolizumab IV, respectively. There was no increase in asthma exacerbations during the interim period between the end of MEA112997 and the start of MEA115666.	

3.3.2. Benefit Assessment

Study 205203 is an open-label extension study to Study 200622, a 32-week treatment period, randomized, placebo-controlled study during which participants with HES receive either 300mg SC mepolizumab or placebo every 4 weeks. During the 20-week treatment period of Study 205203, all participants will receive active treatment, 300mg SC mepolizumab, every 4 weeks, while they continue with their background HES therapy per SoC. The open-label, active treatment aspect of the study is anticipated to offer clinical benefit to participants based on the effectiveness and safety profile in patients with HES reported in previously completed studies as well as the ongoing mepolizumab HES expanded access which has been active for approximately 10 years [Rothenberg, 2008; Roufosse, 2013; Stein, 2008; Duncan, 2015].

During Study 205203, investigators may adjust the participants' background HES therapy per SoC starting 4 weeks after the first administration of study treatment. Physician-guided alteration of SoC can be expected since completed Study MHE100185 demonstrated that participants with HES receiving mepolizumab 750mg IV every 4 weeks (84%) were able to reduce the dose of maintenance OCS compared to those receiving placebo (43%) without increased clinical activity of HES [Rothenberg, 2008]. Given long-term toxicity of current HES therapy including OCS, the ability to reduce their background HES therapy per SoC may offer benefit to participants.

In addition, participants will attend monthly visits and therefore may benefit from the additional disease monitoring and interaction with health care professionals.

Study 205203 will provide data on the long-term clinical experience of mepolizumab at 300mg SC every 4 weeks in patients with HES. Given the low prevalence of HES and the requirement to blind the blood eosinophil level during the randomized, placebo-controlled study of mepolizumab, a single registration study of 32-week treatment period, Study 200622, was included in the clinical development plan. Study 205203 will allow gathering clinical experience with mepolizumab up to a total of 52 weeks.

3.3.3. Overall Benefit:Risk Conclusion

Data from mepolizumab preclinical and clinical development programs support the pharmacological action of mepolizumab to neutralize IL-5, and consequently treat conditions associated with eosinophilia, such as HES. To date, the safety profile of mepolizumab has been favorable. Furthermore, there are no safety observations with mepolizumab that would preclude investigation in HES. The Sponsor therefore maintains that investigation of mepolizumab in participants with HES is justified in Study 205203.

4. OBJECTIVES AND ENDPOINTS

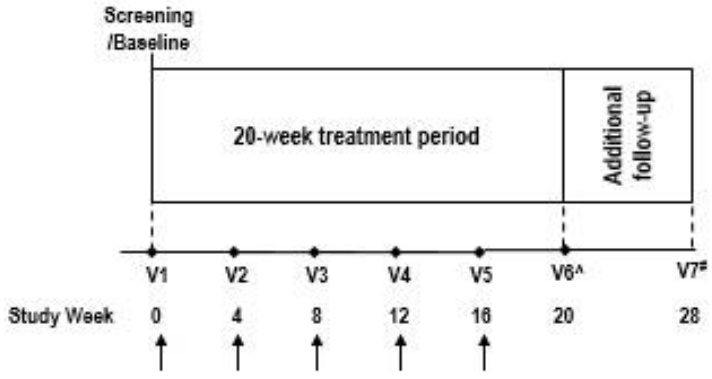
Objectives	Endpoints
Primary - Safety • To describe the long-term safety profile of mepolizumab in participants with HES who took part in Study 200622.	• Adverse events (AEs) [serious and non-serious] • Anti-drug antibody
Other – Safety • To describe the long-term safety profile of mepolizumab in participants with HES who took part in Study 200622.	• Vital signs • 12-lead ECG • Hematological and clinical laboratory tests
Exploratory - Efficacy • To assess the effect of long-term use of mepolizumab on multiple clinical outcomes.	• Rate of HES flare# • Change in the mean daily OCS dose from Weeks 0-4 to Weeks 16-20 • Proportion of participants who achieve a mean daily OCS (prednisone/prednisolone or equivalent) dose of ≤7.5mg during Weeks 16-20
Pharmacodynamic (PD) • To assess the effect of long-term use of mepolizumab on a PD marker	• Blood eosinophil levels

HES flare as defined in Section 9.1.1.

5. STUDY DESIGN

5.1. Overall Design

Figure 1 Study schematic



↑: Mepolizumab treatment (300mg SC per administration)
V: Visit
^: Participants who continue with mepolizumab treatment via mepolizumab HES expanded access after Study 205203 will have the last assessment on Week 20 (Visit 6).
#: Participants who do not continue with mepolizumab via MHE104317/MHE112562 after Study 205203 will have additional follow-up 12 weeks after the last dose (Visit 7).

This is a multi-centre, open-label extension, 20-week treatment period, safety study of mepolizumab in adolescent and adult participants with HES who took part in the phase 3 Study 200622 (Figure 1).

Study 200622 participants who meet one of the following criteria will be screened to continue with Study 205203:

i. Completion of the 32-week treatment period in Study 200622,

or

ii. If the participant was withdrawn from study treatment prematurely during the 200622 study, but continued in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization.

Eligible participants will receive 300mg SC mepolizumab every 4 weeks starting approximately 32 weeks after the first dose of study treatment in Study 200622. In this OLE Study 205203, the final dose of mepolizumab will be administered at Visit 5 (Week 16). Assessments during the Visit 6 (20 weeks after first dose and 4 weeks after the last dose) will complete the study treatment period.

During Study 205203, investigators will be blinded to the blood eosinophil count (Section 12.2) for the sample collected at Visit 1 (1st dosing visit), after which blood eosinophil counts will be unblinded starting at Visit 2. Investigators may adjust the participants' background HES therapy per standard of care starting at Visit 2 (approximately 4 weeks after the first dose).

Participants who complete assessments at Visit 6 (Week 20) may continue with mepolizumab treatment via mepolizumab HES expanded access (e.g., MHE104317, MHE112562), where local regulation permits. Study 205203 participants who do not continue with mepolizumab HES expanded access will have an additional follow-up assessment at Visit 7 (28 weeks after first dose and 12 weeks after the last dose of mepolizumab).

5.2. Number of Participants

Approximately 80 participants will be randomized in the initial recruitment phase for Study 200622. The proportion of participants that have an HES flare will be monitored and the total number of participants randomized may be increased if the blinded overall rate is predicted to be <30%. The sample size may be increased up to a maximum of 120 participants in total. Participants who completed required assessments for 32 weeks starting from randomization in Study 200622 may be evaluated for eligibility to participate in Study 205203.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

5.4. Scientific Rationale for Study Design

The study treatment duration for the phase 3, Study 200622 is 32 weeks. This treatment duration was considered adequate to demonstrate the treatment effect of mepolizumab compared to placebo. However, it was not extended beyond 32 weeks in order to minimize the duration of time that investigators are blinded from blood eosinophil counts which are used in SoC to manage patients with HES. The OLE Study 205203 will provide continuous data for up to 52 weeks (32 weeks 200622 plus 20 weeks 2005203) for 200622 participants who had been assigned to mepolizumab, and will provide additional 20 week mepolizumab exposure data for participants who received placebo during 200622

During the phase 3, randomized, placebo-controlled Study 200622, the same regimen of HES therapy is maintained throughout the 32-week study treatment period unless there is worsening of symptom(s) that requires an increase in therapy. A reduction in dose of HES therapy for safety reasons, with return to the original dosing regimen if possible, is permitted in consultation with the GSK Medical Monitor. By restricting titration of background therapy(ies) which could impact the subject's clinical status, the phase 3 study design mitigates a confounding element that could impact the assessment of the primary endpoint, HES flare. HES flare is defined as HES-related clinical manifestation resulting in therapy escalation due to symptoms or receipt of two or more courses of blinded active OCS. In the OLE Study 205203, the primary objective is to describe the

long-term safety profile of mepolizumab in participants with HES while all participants receive active treatment. Therefore, during Study 205203, participants' HES SoC therapy may be adjusted starting 4 weeks after the first dose of mepolizumab.

5.5. Dose Justification

Based on the goal of obtaining up to 52-week clinical data at the 300mg SC every 4 weeks regimen in participants with HES, the dose of mepolizumab in Study 205203 will remain as 300mg SC every 4 weeks continued from the preceding Study 200622. The maintenance of the 300mg SC mepolizumab dose every 4 weeks during Study 205203 will help further characterize the long-term safety profile of mepolizumab and provide additional data on the clinical benefit in HES patients.

6. STUDY POPULATION

Participants will be evaluated based on the following study entry criteria detailed in Section 6.1 and Section 6.2. Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

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

Study 200622 requirements

1. Age 12 years and older participants who were enrolled in Study 200622.

   To be considered for Study 205203, Study 200622 participants must have completed 32-week assessments since randomization:

   (i) Completion of the 32-week treatment period in Study 200622

   OR

   (ii) If the participant was withdrawn from study treatment prematurely during the 200622 study, but continued in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization.

Sex

2. Male or female

   Female participants:

   A female participant who meets one of the following conditions:

   (i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

   OR

   (ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 at least 30 days prior to the first dose of study treatment and until 16 weeks after the last dose of study treatment.

Positive benefit:risk ratio

3. The treating physician must confirm a positive benefit/risk ratio. The anticipated clinical benefit from mepolizumab must outweigh any potential safety or tolerability risk in Study 205203.

Informed consent

4. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

Medical conditions

1. Participants with any history of hypersensitivity to any monoclonal antibody (including mepolizumab)
2. Participants with current malignancy or malignancy that developed during Study 200622.

   NOTE:

   - Participants who had localized localized carcinoma (i.e., basal or squamous cell) of the skin which was resected for cure will not be excluded.
3. Participant who is pregnant or breastfeeding.

   NOTE:

   - Participants should not be considered for continued treatment if they plan to become pregnant during the course of treatment with mepolizumab.
4. Participant who has other clinically significant medical conditions uncontrolled with SoC therapy not associated with HES, e.g., unstable liver disease, uncontrolled cardiovascular disease, ongoing active infectious disease

   NOTE:

   - Participants with recent parasitic (helminth) infections will be excluded from the study or required to be adequately treated for helminth infections before initiation of mepolizumab.
5. Participants with QTc >450 msec or QTc > 480 msec in participants with bundle branch block based on local EGC reading

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read.

- The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.

6. Liver abnormality/disease:

   - Participants who discontinue study treatment based on liver chemistry stopping criteria during Study 200622
   - Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

     NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.

Prior/concurrent clinical study experience

7. Other investigational product/clinical study:

   - Participants who have received treatment with an investigational agent (biologic or non-biologic) within the past 30 days or 5 drug half-lives whichever is longer, prior to the first dose, other than Study 200622 study treatment. The term "investigational" applies to any drug not approved for sale for the disease/indication to treat in the country in which it is being used or investigational formulations of marketed products
   - Participants who are currently participating in any other interventional clinical study

8. Participant had an adverse event (serious or non-serious) considered related to study treatment while participating in Study 200622 which resulted in permanent withdrawal of study treatment.

6.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but subsequently have not received any study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only upon approval by the GSK Medical Monitor.

7. TREATMENTS

Study treatment is defined as any investigational treatment intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name	SB240563 (mepolizumab)
Dosage formulation	Mepolizumab 100 mg vial for injection contains target quantities of 10.3 mg sodium phosphate dibasic heptahydrate, 0.96 mg polysorbate 80 and 230.4 mg xucrose per vial
Unit dose strength(s)/Dosage level(s)	3 vials (100mg/vial) per administration
Route of Administration	3 SC injections per administration
Dosing instructions	Participants will be dosed with three 100 mg SC injections every 4 weeks. Injections should be administered into the abdomen, upper arm, or thigh.
Packaging and Labeling	Study Treatment will be provided in a vial. Each vial will be labelled as required per country requirement.
Manufacturer	GlaxoSmithKline

Participants will be monitored during SC administration and for 1 hour after the first three administrations and then follow monitoring policies for the center. Such monitoring will include general safety monitoring including monitoring for both systemic reactions (e.g., hypersensitivity) and local site reactions. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of mepolizumab, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the subject including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.

7.2. Method of Treatment Assignment

Study treatment will be dispensed at the study visits summarized in SOA.

7.3. Blinding

This is an open-label treatment study. All eligible participants will receive 300mg SC mepolizumab every 4 weeks for a total of 5 doses during the 20-week treatment period.

During Study 205203, investigators and the study team will be blinded to the blood eosinophil count (Section 12.2) for the sample collected at Visit 1 (1st dosing visit), after which blood eosinophil counts will be unblinded starting at Visit 2.

Blinding to previous treatment assignment as well as blood eosinophil counts in Study 200622 will be maintained until that study has reached DBF.

7.4. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all supply of mepolizumab received and any discrepancies are reported and resolved before use of mepolizumab.
- Only participants enrolled in the study may receive mepolizumab and only authorized site staff may supply or administer study treatment. All supply of mepolizumab must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for mepolizumab accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Under normal conditions of handling and administration, mepolizumab it 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 GSK monitor, Medical Monitor and/or 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.

Mepolizumab must be stored in a secure area under the appropriate physical conditions for the product, which includes storage in a refrigerator or at a temperature of 2-8°C and protected from light. Maintenance of a temperature log (manual or automated) is required. Access to mepolizumab will be limited to the investigator's authorized site staff. Mepolizumab must be dispensed or administered only to participants enrolled in the study and in accordance with the protocol.

7.5. Treatment Compliance

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

- Participants will be dosed at the site directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of mepolizumab and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering mepolizumab.
- Mepolizumab will be administered to participants as 3 SC injections per dosing visit at the site. Administration will be documented in the source documents and reported in the CRF.

7.6. Concomitant Therapy

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

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

Concomitant therapy with another biological therapy (e.g., monoclonal antibodies or IV immunoglobulin therapy) should be discussed with the GSK Medical Monitor prior to beginning therapy. If allowed, therapy should not be administered at the same time as the mepolizumab injection(s) and physicians should take measures to separate administration of another biological therapy as long as possible from administration of mepolizumab.

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

7.7. Treatment after the End of the Study

Participants who complete assessments at Visit 6 (Week 20) in Study 205203 may continue with mepolizumab treatment via mepolizumab HES expanded access (e.g., MHE104317, MHE112562), where local regulation permits.

Participants who prematurely discontinue mepolizumab during Study 205203 will be considered for mepolizumab HES expanded access, if available, 20 weeks after the first dose. This requirement is placed to encourage participants to continue mepolizumab treatment via the OLE Study 205203 rather than immediately transitioning from Study 200622 to mepolizumab HES expanded access where relatively limited data are collected.

8. TREATMENT DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants who discontinue study treatment prematurely (for any reason) should, where possible, continue in the study per protocol (Refer to SoA) until 20 weeks after the first dose of mepolizumab in study 205203 (Visit 7), including the collection of biological

samples for laboratory assessments approximately 4 weeks and 12 weeks after the last dose of mepolizumab.

If a participant experiences an organ-threatening or a life-threatening event, the investigator should discuss continuation of mepolizumab with the GSK Medical Monitor.

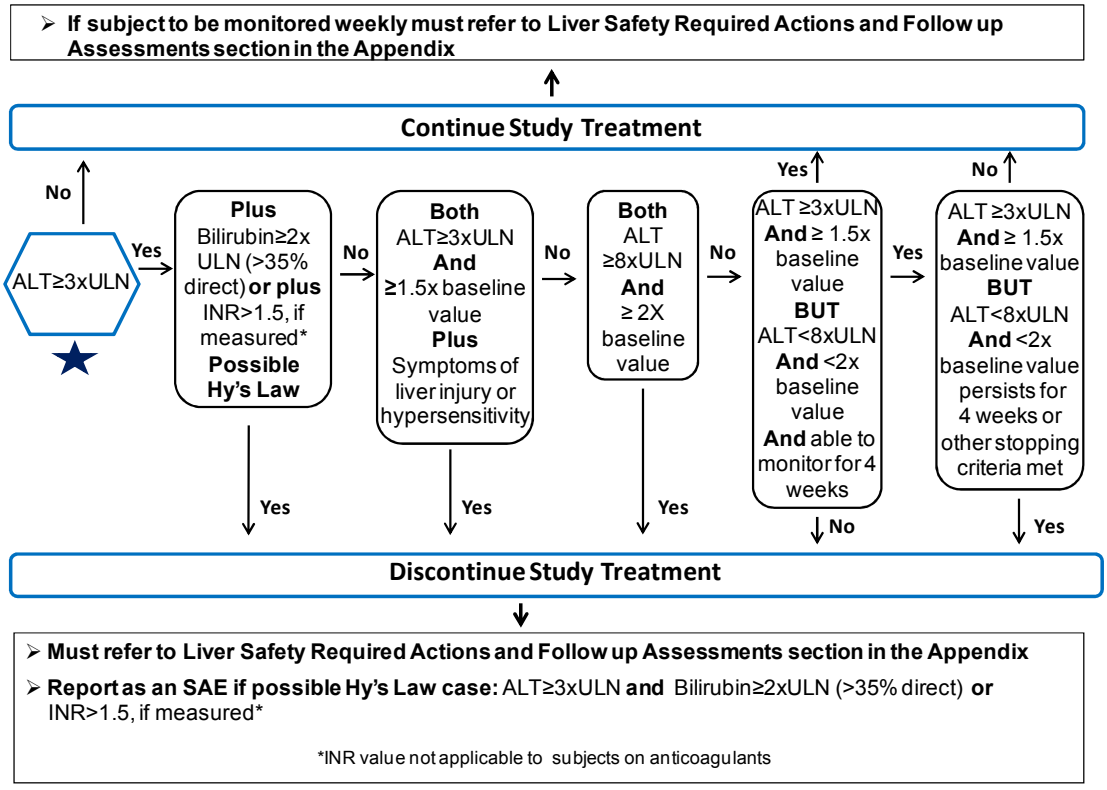
Participants will be withdrawn from treatment with mepolizumab for any of the following reasons:

- **Pregnancy**: Any female subject who becomes pregnant.
- Meet the **liver chemistry stopping criteria** (Section 8.1.1)
- Meet **QTc stopping criteria** (Section 8.1.2).

8.1.1. Liver Chemistry Stopping Criteria

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). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Figure 2 Liver Stopping and Monitoring Event Algorithm



Refer to Section 12.6 for Liver Safety Required Actions and Follow-up Assessments.

8.1.2. QTc Stopping Criteria

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

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

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

8.1.3. Temporary Discontinuation of Mepolizumab

If a participant becomes infected with helminths while receiving mepolizumab and does not respond to anti-helminth treatment, temporary discontinuation of mepolizumab should be considered in consultation with GSK Medical Monitor.

8.1.4. Rechallenge

8.1.4.1. Study Treatment Restart or Rechallenge

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

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA (WD visit and Visit 7 additional follow-up) for data to be collected at the time of withdrawal from the study and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

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

9.1. Efficacy Assessments

9.1.1. HES Flare

A HES flare is defined as an HES-related clinical manifestation based on a physician-documented change in clinical signs or symptoms (worsening symptoms and/or elevated blood eosinophil level) resulting in the need for either of the following:

- An increase from the most recent dose in the maintenance OCS dose (prednisone/prednisolone equivalent) by at least 10mg/day for 5 days

- An increase in or addition of any cytotoxic and/or immunosuppressive HES therapy from/to the most recent dose of HES therapy.

To be considered as an HES flare, the most recent dose of HES therapy must not have changed for at least 4 weeks. This ensures that failed reductions in HES therapy are not misclassified as an HES flare.

The start date for an HES flare will be defined as the date of therapy escalation confirmed by the investigator attributable to an HES-related clinical manifestation.

When a subject experiences an HES flare, the investigator will monitor the change in disease control per routine medical care (e.g., follow-up call) and record the resolution of the flare including the end date. Investigators are encouraged, as medically appropriate, to return the subject's treatment regimen to the level prior to the flare after the flare has resolved.

In the event of disease worsening for which the investigator suspects an HES flare between scheduled clinic visits, when possible, the subject will return to the clinic to have the unscheduled 'Flare' visit assessment completed as described in the SoA. When attending the clinic visit at the time of a suspected HES flare is not possible, the investigator should make every effort to evaluate the subject via telephone and complete the HES Core Assessments (Section 9.1.2). If an escalation of therapy is initiated by a non-study physician, the investigator should confirm that the escalation in therapy is attributable to an HES-related clinical manifestation.

Investigators will be required to record details pertaining to the HES flare event in the CRF from Visit 1 until 20 weeks after the first dose of mepolizumab. This should include details regarding the clinical symptoms resulting in the flare with detail of the required intervention(s), e.g., OCS dose increase, *or* addition or escalation of immunosuppressive or cytotoxic therapy. In addition, all other relevant clinical, laboratory or other diagnostic investigations required to confirm the flare must be captured in the CRF.

The definition of HES flare for this study (205203) is different from that for the preceding, randomized Study 200622. This difference in definitions is due to the requirement during Study 200622 to avoid decreases in background HES therapy that may confound a blinded subject's clinical status. In Study 205203, all participants will receive mepolizumab and investigators will be unblinded to blood eosinophil levels starting 4 weeks after the first dose (Visit 2) so that they may adjust background HES therapy as per SoC.

9.1.2. HES Core Assessments (Clinician Assessment)

Clinical evaluation by the investigator will be guided by the HES Core Assessments, consisting of clinical signs and symptoms that reflect the heterogeneous nature of HES observed in clinical practice. During the study, the investigator will evaluate participants

at each clinic visit using the HES Core Assessments and determine whether worsening of signs/symptoms supports an increase in HES therapy. In addition, to further characterize the basis for determination of flare and increase in therapy, the investigator will prepare a narrative for each HES flare.

The HES Core Assessments will characterize each subject's clinical manifestations at baseline and monitor for changes throughout the study. The investigator will be asked to rule out other possible etiologies for the change in clinical symptoms, such as an infection, prior to diagnosing an HES flare. For the "others" category in Table 1, specific components of the physical exam will be used as part of the baseline core assessments and throughout the study to monitor for the presence or absence of changes in exam findings. Findings of the HES Core assessments will be recorded in the electronic device.

Table 1 HES Core Assessments

Symptoms	Assessment
Constitutional	
Fatigue Pain (including but not limited to muscle, joint, general pain) Angioedema (swelling under the skin)	Each symptom rated using a 0-3 scale
Dermatologic	
Rash Itch Hives Others (specify)	Each symptom rated using a 0-3 scale
Gastrointestinal	
Average number of vomiting a day in the past week Average number of diarrhea a day in the past week Average number of stools a day in the past week Abdominal pain Difficulty in swallowing food	Each symptom rated using a 0-3 scale
Respiratory	
Breathing symptoms such as shortness of breath and wheezing	0-3 scale
Dyspnea (shortness of breath)	0-3 scale
Cough	0-3 scale

Symptoms	Assessment
Sinus-related symptoms: Nasal congestion Sinus headache/facial pain/pressure Postnasal drip (drainage down the back of the throat) Purulent rhinorrhea (discoloured & thick nasal discharge) Ear fullness	Each symptom rated using a 0-3 scale
Cardiovascular	
Heart failure classification for functional capacity	Classes I-IV
Heart failure classification for objective assessment	Classes: A-D
Neurologic	
Sensory Motor Cognitive and Mental status change	Each symptom rated using a 0-3 scale
Others	
Vascular, venous, arterial, loss of pulse, splinter hemorrhage, renal failure, splenomegaly, other (specify)	Each identified symptom rated using a 0-3 scale

1. 0-3 scale symptom score: 0 for not present or no impact, 1 for present but minimal impact, 2 for significant impact on daily activities, 3 for incapacitating

9.2. Adverse Events

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

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

- Local injection site reactions
- Systemic reactions

In addition, the information whether an event met the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] and in Section 12.7 will be collected on the AE and SAE CRF pages.

The investigator and any 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 treatment or the study

participation, or that caused the participant to discontinue the study treatment or study participation (see Section 8).

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. 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 treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical

investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 12.9 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 Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

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

9.2.6. Pregnancy

- Details of all pregnancies in female participants that occur from the first dose of study treatment and until at least 16 weeks post-last dose of study treatment will be collected.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 12.5.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of Overdose

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

In the event that mepolizumab is administered more than as detailed in the protocol in terms of dose or frequency, the investigator should contact the GSK Medical Monitor immediately.

9.4. Safety Assessments

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

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the ear nose throat (ENT), Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded..
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Temperature, pulse rate, and blood pressure will be assessed.
- Vital signs will be measured prior to blood draws in a sitting position after 5 minutes rest.

9.4.3. Electrocardiograms

- Details of the cardiac monitoring procedures will be provided by the centralized cardiology service provider.
- All sites will use standardized ECG equipment provided by a centralized external vendor.
- Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times. All ECG measurements will be made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading.
- 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. There will be electronic capture and storage of the data by a validated method, with subsequent transfer to the central laboratory for manual reading and calculation of the electrocardiographic parameters. Paper traces are required to be maintained at the site with other source documents.
- The investigator, a designated sub-investigator, or other appropriately trained site personnel will be responsible for performing each 12-lead ECG. The investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.
- All ECGs will be electronically transmitted to an independent cardiologist (contracted by GSK) and evaluated. The independent cardiologist will be responsible for providing measurements of heart rate, QT intervals and an interpretation of all ECGs collected in this study. A hard copy of these results will be sent to the investigator. The investigator must provide his/her dated signature on the confirmed report, attesting to his/her review of the independent cardiologist's assessment to support the decision regarding the continuation or discontinuation of study treatment based on the ECG results (Section 8.1.2).

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc stopping criteria.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or GSK Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

9.5. Pharmacokinetics

- Blood samples for determination of mepolizumab plasma concentration will be collected prior to dosing at the timepoints indicated in SoA. The actual date and time of each blood sample collection will be recorded.
- Processing, storage and shipping procedures are provided in the laboratory manual.

9.6. Pharmacodynamics

- Blood eosinophil counts will be recorded as part of the standard hematology assessments performed at the visits specified in the SoA.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

9.8.1. Immunogenicity Assessments

- Blood samples will be collected prior to dosing at visits specified in the SoA. Samples will be analysed for the presence of anti-mepolizumab antibodies.

- Processing, storage and shipping procedures are provided in the laboratory manual.

9.8.2. Optional Biomarker Sub-study

With the subject's consent, blood samples will be collected during this study and will be used for the optional biomarker sub-study. In addition, the samples may be used for the purposes of measuring novel biomarkers to identify factors that may influence HES, and/or potentially medically related conditions (e.g., T-cell lymphoma), as well as the biological and clinical responses to study treatment. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with HES conditions that are medically related to HES, and/or the action of study treatment may be identified by application.

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

9.9. Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

There is no sample size calculation for this study. The sample size will be determined by the number of available participants who were randomized in to Study 200622 and are eligible for the current study based on the inclusion and exclusion criteria.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Subjects Enrolled (ASE)	All subjects who sign the ICF and for whom a record exists on the database.
Safety	All participants who take at least 1 dose of mepolizumab (study treatment).

10.3. Statistical Analyses

10.3.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

AEs will be coded using MedDRA coding dictionary and summarised by preferred term. Separate summaries will be provided for all AEs, IP-related AEs, SAEs, events of special interest (including systemic reactions and local injection site reactions) and for AEs leading to permanent discontinuation of IP or withdrawal from the study.

The number of participants with anti-mepolizumab antibodies during the study will be summarized.

Further details of the analysis of safety will be provided in the Reporting and Analysis Plan (RAP).

10.3.2. Efficacy, Pharmacodynamic, and Pharmacokinetic Analyses

Details of the analysis of exploratory efficacy endpoints will be provided in the RAP.

PD analyses will be described in the RAP.

To put into context the result of the immunogenicity assessment PK samples are collected in this study and mepolizumab PK concentrations will be summarized descriptively by immunogenicity status.

10.3.3. Interim Analyses

Interim analysis will be performed as needed in order to provide open-label safety data to inform the risk-benefit assessment of mepolizumab in HES.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ASE	All subjects enrolled
AST	Aspartate transaminase
BP	Blood pressure
CHF	Congestive heart failure
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
CV	Cardiovascular
DBF	Database freeze
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EGPA	Eosinophilic Granulomatosis with Polyangiitis
FAAN	Food Allergy and Anaphylaxis Network
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
hCG	human chorionic gonadotrophin
HES	Hypereosinophilic Syndrome
HF	Heart failure
HPLC	High performance liquid chromatography
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-Treat
LDH	Lactate dehydrogenase

mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligrams
MSDS	Material Safety Data Sheet
Msec	millisecond
NAB	Neutralizing antibodies
NIAID	National Institute of Allergy and Infectious Disease
NYHA	New York Heart Association
NPS	Named Patient Supply
OCS	Oral corticosteroid
OLE	Open-label extension
PCR	Polymerase chain reaction
PCSA	Placebo-controlled severe asthma
PD	Pharmacodynamics
PEF	Peak expiratory flow
PK	Pharmacokinetics
PMS	Post marketing surveillance
PP	Per protocol
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SC	Subcutaneous(ly)
SDAC	Statistical analysis data center
SoA	Schedule of Activities
SOC	System Organ Class
SoC	Standard of care
SRM	Study reference manual
SUSAR	Suspected unexpected serious adverse reactions
TOC	Table of Contents
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
WOCBP	Women of childbearing potential
WBC	White blood cell
WD	Withdrawal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in SoA will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: *Total white cell count*# Neutrophils (absolute and *differential [%]*#) Lymphocytes (absolute and *differential [%]*#) Monocytes (absolute and *differential [%]*#) Eosinophils (*absolute*# and *differential [%]*#) Basophils (absolute and *differential [%]*#)	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones (by dipstick, if locally permitted) • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential [WOCBP])[2] All study-required laboratory assessments will be performed by a central laboratory, with the exception of urine pregnancy tests			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. # (underlined and italicized) indicates the results that will not be sent to the investigators for blinding from the blood eosinophil counts for the samples collected prior to Visit 2.

Investigators, GSK personnel involved in the study, and participants will be blinded to the results of absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%) from the sample collected at Visit 1. This will ensure treatment blinding for Study 200622 of which last dose were given approximately 4 weeks prior to Visit 1 of Study 205203.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH

guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

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

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory

data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report(CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

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

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

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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

the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in 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 with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are 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 sufficiently 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 treatment 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 treatment 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 t GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to ensure sending the data to GSK within 24 hours following knowledge of the SAE. • 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 study treatment/study participation (causality) within 72 hours of SAE entry into the eCRF. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the GSK Medical Monitor by telephone. • Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **GSK Medical Monitor**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

Contraception Guidance

Female participants

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 Table 3.

Table 3 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
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 drug. 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.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized at least 30 days prior to the first dose of study treatment and until 16 weeks after the last dose of mepolizumab

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine (or serum, if locally required) pregnancy test
- Additional pregnancy testing should be performed at monthly intervals during the treatment period and at 4 weeks after the last dose of study treatment and as required locally.

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed and assayed in a certified laboratory OR and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert.

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 treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

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

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

Liver chemistry stopping criteria

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	**Both** ALT ≥ 8xULN **and** ≥ 2X baseline value
ALT Increase	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that 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	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value **and** cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
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 (laboratory assessments performed closest and prior to first dose of study treatment). • **Do not restart/rechallenge** participant with study treatment. • If restart/rechallenge not allowed, permanently discontinue study treatment and may continue participant in the study for any protocol-specified follow up assessments.	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend. • 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 1 week of the liver event[6]. • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia. Note: the mechanism of action of mepolizumab is lowering the eosinophils. • Record the appearance or worsening of clinical symptoms of liver injury, or

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.	hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study 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 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 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 ≥3xULN and ≥ 1.5x baseline value **but** ALT <8x ULN and < 2x baseline value **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, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

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

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

12.7. Appendix 7: Anaphylaxis Criteria

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

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

12.8. Appendix 8: Classification of Heart Failure

Physicians usually classify patients' heart failure according to the severity of their symptoms [American Heart Association, 2014]. The table below describes the most commonly used classification system, the NYHA Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity.

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest.

Class	Objective assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

For Example:

- A patient with minimal or no symptoms but a large pressure gradient across the aortic valve or severe obstruction of the left main coronary artery is classified: Function Capacity I, Objective Assessment D.
- A patient with severe anginal syndrome but angiographically normal coronary arteries is classified: Functional Capacity IV, Objective Assessment A.

12.9. Appendix 9: 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

12.10. Appendix 10: Protocol Amendment History

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

Information regarding the previous amendment is as follows:

Amendment 01 13-JAN-2017

Overall Rationale for the Amendment: To provide the correct EudraCT number in the protocol.

Section # and Name	Description of Change	Brief Rationale
Title Page	Regulatory Agency Identifying Number: EudraCT# was changed from 2014-001232-11 to 2017-000184-32.	The change was made to reflect the correct EudraCT# associated with the protocol.

Numbering of Global Protocol Amendments

Type of Protocol Amendment	Numbering	Type of changes
Global	Amendment 02	New changes for all
Global	Amendment 01	New changes for all

Document History Table for Global Protocol Amendment

DOCUMENT HISTORY	
Document	***Date of Issue***
Amendment 02	16-Nov-2017
Amendment 01	13-Jan-2017
Original Protocol	02-Nov-2016