TITLE PAGE

Protocol Title: A Phase 3, 52-week, open-label, single arm study to investigate the efficacy and safety of mepolizumab SC in participants aged 6 to 17 years with hypereosinophilic syndrome.

Protocol Number: 215360/ Amendment 04

Compound Number or Name: SB240563

Brief Title: Study in Paediatrics with HypEREosinophilic syndrome (SPHERE)

Study Phase: Phase 3

Acronym: SPHERE

Sponsor Name and Legal Registered Address:

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

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

Sponsor Signatory

Anna Leslie
Clinical Development Director

Regulatory Agency Identifying Number(s):

IND: 11295

EudraCT: 2021-000933-15

EU CT number: 2023-510110-36-00

Pediatric investigational plan number: EMEA-000069-PIP01-07-M09

Approval Date: 16 Dec 2024

Based on TMF-14732712 Protocol v3.0.

Protocol Amendment 4 Investigator Agreement

- **To assume responsibility for the proper conduct of the study at this site.**
- **That I am aware of and will comply with GCP and all applicable regulatory requirements.**
- **That I will comply with the terms of the clinical study site agreement.**
- **To ensure that all persons assisting me with the study are adequately informed about the** GSK **study intervention and other study-related duties and functions as described in the protocol.**
- **To cooperate with representative(s) of** GSK **in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.**

Study identifier	215360
Abbreviated title	Study in Paediatrics with HypEREosinophilic syndrome (SPHERE)
EudraCT number	2021-000933-15
EU CT number	2023-510110-36-00
Approval date	16 Dec 2024
Title	A Phase 3, 52-week, open-label, single arm study to investigate the efficacy and safety of mepolizumab SC in participants aged 6 to 17 years with hypereosinophilic syndrome.
Investigator name	
	_____
Signature	
	_____
Date of signature	
(DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 04	16 Dec 2024	TMF-20082402
Amendment 03	21 August 2023	TMF-16349402
Amendment 02 ITA 1	09 June 2022	TMF-14643220
Amendment 02	09 June 2022	TMF-14643214
Amendment 01 ITA 1	22 March 2022	TMF-14489137
Amendment 01	02 August 2021	TMF-13865997
Original Protocol	16 April 2021	TMF-12458678

Amendment 04 (16 Dec 2024)

This amendment is considered to be substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC and EU Clinical Trial Regulation No. 536/2014 of the European Parliament of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This protocol has been amended to change the number of participants, clarified the end of study visits for participants who do not enter the expanded access program (EAP), the prohibited medications (anti-IL-5 and anti-IL-5-receptor therapies), and the T-cell profile sample.

List of main changes in the protocol and their rationale:

Section # and title	Description of Change	Brief Rationale
Sponsor signatory	Updated new sponsor signatory	Change in sponsor signatory
Section 1.1 Synopsis Section 3. OBJECTIVES AND ENDPOINTS Table 3 Objectives and Endpoints	Updated Objectives, Endpoints, and Estimands, by the removal of assessment of biological response to mepolizumab in participants aged 6 to 17	Removal of one of the endpoint regarding peripheral blood genomic and transcriptomic analysis

Section # and title	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Added the missing concomitant medication check on follow up visit	Updated the Schedule of Activities Table
Section 1.3 Schedule of Activities Table 1, Footnotes Section 10.2 Clinical Laboratory Tests Table 8, Footnotes	Updated the footnote 14 in Table 1 Updated the footnote numbers 23, 24 and 25. as it was erroneously captured Updated the footnote 1 in Table 8	To provide clarification on Local lab eosinophil count results will be entered in eCRF Updated the footnotes to rectify the error
Table 3 Objectives and Endpoints Section 8.1.3 Reduction of Use of OCS, Immunosuppressive and/or Cytotoxic HES Therapy	Minor clarification regarding the outcome and population of interest when assessing reductions in immunosuppressive and/or cytotoxic HES therapy at Week 52	Clarified that the outcome of interest is those participants that are taking and not taking immunosuppressive and/or cytotoxic HES therapy at Week 52. Clarified that the population of interest is those participants that are taking immunosuppressive and/or cytotoxic HES therapy at baseline.
Section 4.1 Overall Design Section 5 Study Population Section 9.2 Sample Size Determination Section 10.1.4 Recruitment Strategy	Sample size reduced from 25 participants to 15 participants	Clarification of the change in sample size requirements, with at least 11 participants to be children (aged 6 to 11 years) and at least 4 participants to be adolescents (aged 12 to 17 years
Section 4.4 End of Study (EOS) Definition	Clarification of the EOS for participants who enter or not enter expanded access program (EAP)	Updated the End of Study Definition
Section 6.8 Concomitant Therapy	Updated the concomitant medication with the prohibited medications	To provide additional information on permitted and prohibited concomitant medications
Section 8.3.4 Regulatory Reporting Requirements for SAEs	Update the section to provide an assessment of causality by the investigator	To comply with the new GSK protocol template requirements
Section 8.3.8 Medical Device Deficiencies	Provided information on regarding the usage of medical devices	To comply with the new GSK protocol template requirements

Section # and title	Description of Change	Brief Rationale
Section 8.7 T-cell profile	Updated the section for using the results of T-cell profile during Visit 2	To provide clarity on the use of results of T-cell profile
Section 9.4.3 Other Endpoints	Re-instating text regarding the handling of the exploratory endpoint "Taking immunosuppressive and/or cytotoxic HES therapy at Week 52 in participants that are taking immunosuppressive and/or cytotoxic HES therapy at baseline" Clarification added regarding the annualised flare rate during the study to be compared with the annualised flare rate in the year prior to Screening (Visit 1) for each patient.	Clarified wording that premature study withdrawal will be considered as a treatment failure within the assessment of this dichotomous exploratory endpoint. Additional wording inserted to further clarify on the reporting of this exploratory endpoint on changes in HES flare rate.
Section 10.1.3 Informed Consent and Assent Process	Addition of a paragraph on the time of storage of collected samples	To comply with the new GSK protocol template requirements
Section 10.1.5.Data Protection	Statement regarding protection of the personal data and GSK internal policy was added	To comply with the new GSK protocol template requirements
Section 10.1.7 Dissemination of Clinical Study Data	Updated the section as per the new protocol template	To comply with the new GSK protocol template requirements
Section 10.1.8 Data Quality Assurance	Updated a statement regarding the storage of source data by external body	To comply with the new GSK protocol template requirements
Section 10.1.9 Source Documents	Updated a statement regarding recording and sharing of source data	To comply with the new GSK protocol template requirements
Section 10.1.11 Publication Policy	Updated a statement regarding publication of results	To comply with the new GSK protocol template requirements
Section 10.3.5 Reporting of SAE to GSK	Addition of statement regarding classification of spontaneous ICSRs.	To comply with the new GSK protocol template requirements
Country Specific Requirements Appendix	Removed appendix stating country specific requirements in Italy	Italy to no longer be included in study.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, 52-week, open-label, single arm study to investigate the efficacy and safety of mepolizumab SC in participants aged 6 to 17 years with hypereosinophilic syndrome.

Brief Title: Study in Paediatrics with HypEREosinophilic syndrome (SPHERE)

Rationale:

Hypereosinophilic syndrome (HES) is a group of rare haematological disorders without a known cause in which eosinophils are overproduced in the bone marrow for prolonged periods of time. The goal of HES treatment is to relieve symptoms and to reverse or delay progression of any further organ damage caused by activated eosinophils. Mepolizumab has been shown to be efficacious and well tolerated in patients with HES.

The purpose of this study is to investigate the efficacy and safety of mepolizumab SC in children (aged 6 to 11 years) and adolescents (aged 12 to 17 years) with HES who are receiving standard of care (SoC) therapy. The primary objective of the study is to evaluate the efficacy of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years with HES.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years with HES	• Frequency of HES flares over the 52-week study treatment period
Secondary	
• To assess the effect of mepolizumab SC given every 4 weeks on the change in oral corticosteroid (OCS) dose in participants aged 6 to 17 years with HES that are taking OCS at baseline	• Change in the mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 to Weeks 48 to 52 • Reduction of ≥50% in mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52 • Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52
• To assess the effect of mepolizumab SC given every 4 weeks on the change in oral corticosteroid (OCS) dose in participants aged 6 to 17 years with HES	• Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52

Objectives	Endpoints
• To assess the efficacy of mepolizumab SC given every 4 weeks on fatigue in participants aged 12 to 17 years with HES	• Change from baseline in fatigue severity based on weekly average score of Brief Fatigue Inventory (BFI) item 3 (worst level of fatigue during past 24 hours) for Week 52
• To evaluate the immunogenicity of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years with HES	• Occurrence of anti-drug antibodies (ADA) and neutralising antibodies (NAb)
• To assess the effect of long-term use of mepolizumab SC on a pharmacodynamics (PD) marker in participants aged 6 to 17 years with HES.	• Ratio to baseline in absolute blood eosinophil count at discrete time points during the 52-week study treatment period
• To assess the pharmacokinetics (PK) of mepolizumab SC in participants aged 6 to 17 years with HES	• Mepolizumab plasma concentration at discrete time points during the 52-week study treatment period
Other	

CCI

[redacted]

Objectives	Endpoints
CCI [redacted]	
• To evaluate the safety of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years with HES	• Occurrence of adverse events (AEs) and serious adverse events (SAEs) • Change from baseline in vital signs (blood pressure, heart rate and temperature) • Change from baseline in 12-lead electrocardiogram (ECG) • Haematological and clinical laboratory tests

Primary estimand

The primary clinical question of interest is: What is the rate of HES flares during 52 weeks of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years, regardless of treatment discontinuation for any reason and regardless of changes in background therapy?

The estimand is described by the following attributes:

- Population: participants with HES aged 6 to 17 years with or without maintenance SoC therapy
- Treatment condition: Mepolizumab given every 4 weeks in addition to SoC
- Variable/endpoint: frequency of HES flares over 52 weeks
- Summary measure: annualised rate of HES flares

- Intercurrent events:
  - Study treatment discontinuation – treatment policy strategy
  - Change in background HES medication (other than changes due to a clinically documented flare) - treatment policy strategy
- Rationale for estimand:
  - Interest lies in the rate of flares when medication is taken for the entire study duration. For participants discontinuing study medication or changing background medication, use of a treatment policy strategy recognises that this could be due to an unfavourable cause.

Secondary efficacy estimands

Secondary efficacy estimands address changes in OCS use and effects on fatigue severity.

Estimands for changes in OCS use will use the subpopulation of participants with HES aged 6 to 17 years who are taking OCS at baseline. Treatment condition will be the same as for the primary estimand. The following 3 endpoints and summary measures will be used:

1. Endpoint: Change in the mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 to Weeks 48 to 52; summary measure: mean across participants.

2. Endpoint: Reduction of ≥50% in mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52; summary measure: proportion of participants with this reduction.

3. Endpoint: Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52; summary measure: proportion of participants with this level of OCS usage.

For the intercurrent event of study treatment discontinuation, a treatment policy strategy will be used. Use of OCS is part of the endpoint (composite strategy). Other changes in background HES medication will use a treatment policy strategy.
An additional estimand for changes in OCS use will use the whole population of participants with HES aged 6 to 17 years. Treatment condition will be the same as for the primary estimand. The following endpoint and summary measure will be used:

- Endpoint: Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52; summary measure: proportion of participants with this level of OCS usage.

For the intercurrent event of study treatment discontinuation, a treatment policy strategy will be used. Use of OCS is part of the endpoint (composite strategy). Other changes in background HES medication will use a treatment policy strategy.

The secondary estimand for fatigue severity will use the subpopulation of participants with HES aged 12 to 17 years. Treatment condition will be the same as for the primary estimand. A treatment policy strategy will be used for the intercurrent events of study treatment discontinuation and changes to background HES therapy. The endpoint will be the change from baseline in weekly average score of the BFI item 3 (worst level of fatigue during past 24 hours) for Week 52 and the summary measure will be the mean value.

Overall Design:

This is a 52-week, open-label, single arm, multicentre study of SC mepolizumab in children and adolescent participants with HES receiving SoC therapy.

Brief Summary:

The purpose of this study is to investigate the efficacy and safety of SC mepolizumab in paediatric participants aged 6 to 17 years with HES.

Approximately 15 participants who are on a stable dose of HES therapy for at least 4 weeks prior to Visit 2 will be enrolled. All eligible participants will receive mepolizumab, with the first dose administered at Visit 2, and subsequent doses administered every 4 weeks over a treatment period of 52 weeks (with a last dose at 48 weeks).

Concomitant SoC therapy may be adjusted as needed from 4 weeks after the first dose of mepolizumab. All participants will be managed during the study according to routine medical care.

All participants will attend a study-site visit at Screening (Visit 1), Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 24 (Visit 8), and the Week 52 exit visit (Visit 15). The other study visits may be performed remotely where applicable country and local regulations allow. Home healthcare services may also be utilised to support these activities where local regulations and infrastructure allow. The final visit of the treatment period will be at Week 52. There is a follow-up visit at Week 60, 8 weeks after the Week 52 visit (12 weeks after the last dose of mepolizumab).

Eligible participants may enter an expanded access program (EAP), where available, immediately after completion of the 52-week study period. Participants who withdraw from the study prematurely will not be considered for an EAP.

Number of Participants:

The number of participants was selected based on practical considerations. At least 15 participants aged 6 to 17 years will be enrolled and receive at least 1 dose of mepolizumab. Due to the rare nature of HES in paediatrics, there is minimal data available to predict the age distribution in the study. CCI [redacted]

Note: "Enrolled" means a participant, or their legally acceptable representative, agrees to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

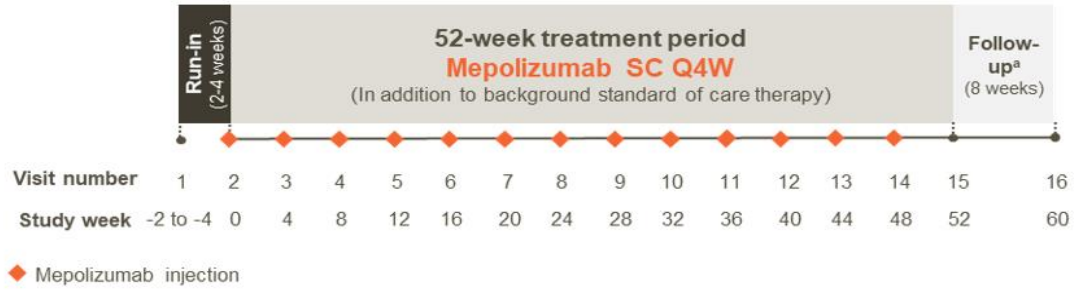
All participants will receive active treatment with mepolizumab SC injection every 4 weeks over a treatment period of 52 weeks (with last dose at 48 weeks). CCI [redacted]

[redacted]

Data Monitoring/ Other Committee: An Independent Data Monitoring Committee (IDMC) will be utilised in this study.

1.2. Schema

Figure 1 Schema of Study Design



[a]Participants who enrol in an expanded access program (EAP) of mepolizumab are not required to have a follow-up visit.

1.3. Schedule of Activities (SoA)

The Schedule of Activities (SoA) is presented in Table 1.

Table 1 Schedule of Activities

Procedures	Screen	Treatment Period and Exit Visit[1]															Early discontinuation /Withdrawal Visit		Follow-up
Study visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 Exit visit	Flare[2]	Discontinue from study treatment Visit (replacing visits 2-15)[3]	Withdrawal Visit	16
Study week	-2 to -4	0	4 (±7 days)	8 (±7 days)	12 (±7 days)	16 (±7 days)	20 (±7 days)	24 (±7 days)	28 (±7 days)	32 (±7 days)	36 (±7 days)	40 (±7 days)	44 (±7 days)	48 (±7 days)	52 (±7 days)				~12 wks After last dose (±7 days)
Informed consent[4]	X																		
Eligibility assessments																			
Inclusion/Exclusion criteria	X	X																	
Demography/childbearing status assessment	X																		
Medical and treatment history	X																		
Parasite screening[5]	X																		
Physical examination including height and weight	X							X							X				
Efficacy assessments																			
CCI [redacted]																			
Concomitant medications including OCS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]																			
BFI item 3[6]		→	→	→	→	→	→	→	→	→	→	→	→	→	→		→		
CCI [redacted]																			

Procedures	Screen	Treatment Period and Exit Visit[1]															Early discontinuation /Withdrawal Visit		Follow-up
Study visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 Exit visit	Flare[2]	Discontinue from study treatment Visit (replacing visits 2-15)[3]	Withdrawal Visit	16
Study week	-2 to -4	0	4 (±7 days)	8 (±7 days)	12 (±7 days)	16 (±7 days)	20 (±7 days)	24 (±7 days)	28 (±7 days)	32 (±7 days)	36 (±7 days)	40 (±7 days)	44 (±7 days)	48 (±7 days)	52 (±7 days)				~12 wks After last dose (±7 days)
CCI																			
Safety assessments																			
AE/SAE assessment	X[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[12]	X	X						X							X	X		X	
ECG	X														X	X			
Laboratory assessments[13]																			
Haematology with differential	X[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical and liver chemistry	X	X			X			X			X			X		X	X[15]	X	
Pregnancy test[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[17]	X	X
Urinalysis[18]	X														X		X[15]	X	
Hepatitis serology[19]	X																		
Total IgE		X																	
F/P status[20]	X																		
T-cell profile	X																		
Immunogenicity		X						X							X		X[21]	X	X
PK sample			X					X							X		X[22]	X	
IL-5		X																	
Investigational product																			
Study treatment administration[23]		X	X	X	X	X	X	X	X	X	X	X	X	X					

Procedures	Screen	Treatment Period and Exit Visit[1]															Early discontinuation /Withdrawal Visit		Follow-up
Study visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 Exit visit	Flare[2]	Discontinue from study treatment Visit (replacing visits 2-15)[3]	Withdrawal Visit	16
Study week	-2 to -4	0	4 (±7 days)	8 (±7 days)	12 (±7 days)	16 (±7 days)	20 (±7 days)	24 (±7 days)	28 (±7 days)	32 (±7 days)	36 (±7 days)	40 (±7 days)	44 (±7 days)	48 (±7 days)	52 (±7 days)				~12 wks After last dose (±7 days)
eCRF and eDiary																			
Register visit in IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
eDiary registration and training	X																		
Dispense (D)/collect (C) eDiary	D[24]														C			C	
Review of eDiary[25]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	

Abbreviations: AE, adverse event; BFI, Brief Fatigue Inventory; ECG, electrocardiogram; eCRF, electronic case report form; F/P, FIP1L1-PDGFRα fusion tyrosine kinase gene translocation; HCRU, healthcare resource utilisation; HES, hypereosinophilic syndrome; IgE, Immunoglobulin E; IL-5, Interleukin-5; IVRS Interactive Voice Response Systems; OCS, oral corticosteroid(s); CCI [redacted]; RNA, ribonucleic acid; SAE, serious adverse event; CCI [redacted].

1. Activities that will be performed only in clinic are greyed out. All participants will need to attend a clinic visit at Screening (Visit 1), Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 24 (Visit 8), and the Week 52 exit visit (Visit 15). A Flare Visit follows routine medical practice. The other visits may be performed remotely where applicable country and local regulations and infrastructure allow. Eligibility criteria assessment data will all be captured on site. Data from efficacy assessments other than echocardiogram, ECG, and spirometry will be captured digitally via electronic devices and teleconferences or on site. Echocardiogram, ECG, and spirometry data will only be captured at site visits. Laboratory assessments other than haematology with differential, clinical and liver chemistry, pregnancy test, and PK samples are captured on site.
2. Assessments will be collected when possible depending on the clinical status during worsening of symptoms between scheduled clinic visits to evaluate for a HES flare. 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 participant via telephone and complete the HES Core assessments v2.
3. Subjects who prematurely discontinue study treatment will continue to attend 4-weekly scheduled Discontinuation Visits completing assessments as indicated. Participants who discontinue study treatment are not required to perform a Follow-up visit, unless they have not completed 12 weeks after last dose immunogenicity assessment within the 52 week study period.
4. Informed consent must be obtained prior to starting Visit 1 procedures.
5. Parasitic screening is only required in countries with high-risk or for participants who have visited high-risk countries in the past 6 months. Sites should use local laboratories.

6. CCI [redacted]
8. When a respiratory flare is suspected during the study period based on investigator's judgement.
9. CCI [redacted]
10. When a CV flare is suspected during the study period based on investigator's judgement.
11. Only SAEs that are considered related to study procedures are to be collected from the time of signing informed consent.
12. Vital sign measurements will include temperature, systolic and diastolic blood pressure, and heart rate.
13. During the treatment period, all laboratory samples should be obtained pre-dose.
14. Eosinophil count samples for the screening visit only may be analysed by local labs if required. If a local sample is required, it is important that a sample for central analysis is obtained at the same time. Local lab eosinophil count results performed at the screening visit will be entered to the eCRF. If local lab samples are taken, a second sample will also be sent for central testing. The higher of the eosinophil cell count values is to be used to fulfil the entry criteria for enrolment.
15. Do not perform for each discontinuation visit, follow test frequency of Treatment Period schedule visit 2-15.
16. Negative urine pregnancy test result must be confirmed prior to dosing in female participants of reproductive potential. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
17. Pregnancy testing is only required until the end of systemic exposure, 12 weeks after the last dose.
18. Urine tests are done locally using dipstick. If found abnormal, the urine sample will be sent to the central laboratory for further testing.
19. If test was performed within 3 months prior to Visit 2, testing at Screening is not required. Test required are hepatitis B surface antigen and hepatitis C antibody. Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA test is obtained.
20. If no documented results are available.
21. For participants who discontinue treatment immunogenicity is to be performed 4 and 12 weeks after the last dose only.
22. For participants who discontinue treatment PK is to be performed 4 weeks after last dose only.
23. The date and time of the administration of study treatment will be recorded in the eCRF.
24. CCI [redacted]
25. Review AEs and participant questionnaires, identify HES flares and check questionnaire compliance.

2. INTRODUCTION

2.1. Study Rationale

Hypereosinophilic syndrome (HES) is a group of rare haematological disorders without a known cause in which eosinophils are overproduced in the bone marrow for prolonged periods of time. The sustained overproduction of eosinophils in the bone marrow results in high blood eosinophil counts (eosinophilia). When activated eosinophils from the bloodstream infiltrate various tissues, they cause inflammatory tissue damage and dysfunction. HES is only diagnosed when organ damage and/or dysfunction are present. The current definition and diagnosis of HES in patients uses the following criteria: (1) blood eosinophilia of >1500 eosinophils/µL on 2 examinations (at an interval ≥1month, except in case of life-threatening organ damage when diagnosis can be made immediately) and/or tissue eosinophilia; (2) organ damage and/or dysfunction attributable to tissue eosinophilia; and (3) exclusion of other disorders or conditions as the major reason for organ damage [Valent, 2012].

Mepolizumab

Eosinophilia is central to the pathophysiology of HES and interleukin-5 (IL-5) is a key cytokine regulating the lifecycle of the eosinophil. Neutralisation of IL-5 with an anti-IL5 monoclonal antibody, therefore, offers a potential therapeutic option for HES.

Mepolizumab is a humanised monoclonal antibody (immunoglobulin G1 [IgG1], kappa) that is specific for human IL-5. Mepolizumab blocks binding of human IL-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, such as eosinophilic asthma, HES, eosinophilic granulomatosis with polyangiitis (EGPA), and chronic rhinosinusitis with nasal polyps (CRSwNP), a consistent reduction in blood eosinophil counts is observed in association with mepolizumab administration, with concomitant clinical improvement [Ortega, 2014; Pavord, 2012; Roufosse, 2020; Han, 2020; Wechsler, 2017]. Mepolizumab 300 mg SC administered every 4 weeks was recently approved in the United States, the European Union, and other countries for the treatment of HES.

Phase 3 Study 200622

In the pivotal Phase 3 study, 108 participants aged ≥12 years were treated for 32 weeks with either mepolizumab 300 mg SC or placebo SC every 4 weeks in addition to their stable HES standard of care (SoC) therapy. In this trial, mepolizumab 300 mg administered SC every 4 weeks was significantly effective in reducing HES flares, fatigue severity, and blood eosinophil counts compared with placebo when added to SoC therapy. CCI [redacted]

CCI [redacted]

Open-label Extension Study 205203

During the open-label extension (OLE) study, CCI [redacted] were treated with mepolizumab 300 mg SC every 4 weeks for 20 weeks. CCI [redacted]

The purpose of this study is to investigate the efficacy and safety of mepolizumab SC in children (aged 6 to 11 years) and adolescents (aged 12 to 17 years) with HES who are receiving SoC therapy.

2.2. Background

HES is usually diagnosed in young adults to middle-aged patients between the ages of 20 and 50 years, therefore there are fewer cases of HES that have been described in the paediatric population. The overall prevalence of HES in children and adolescents is unknown. Most published data on paediatric HES are primarily composed of case reports. One study in the United States reported that the prevalence of hypereosinophilia in persons younger than 18 years was 31.4 per 100,000 persons. In this study, 176 participants with hypereosinophilia were identified and only 12 participants (7%) were diagnosed with HES [Burris, 2019].

The clinical manifestations of HES vary from one patient to another and depend on target-organ infiltration by eosinophils [Roufosse, 2007]. In a large multinational cohort study [Ogbogu, 2009] and in the National Institutes of Health (NIH) study [Williams, 2016], the most common clinical manifestations in adult and paediatric cases were dermatologic (e.g., erythematous skin lesions, rash, and urticaria) and pulmonary manifestations (e.g., cough, dyspnoea, and shortness of breath), followed by gastrointestinal manifestations (e.g., diarrhoea, nausea, and abdominal pain). Pulmonary manifestations were more common among adults while constitutional (e.g., fever, weakness, and fatigue) and gastrointestinal manifestations were more common among the paediatric population [Williams, 2016].

Current treatment and unmet medical need

The goal of HES treatment is to relieve symptoms and to reverse or delay progression of any further organ damage caused by activated eosinophils. The current treatment approach is based on reduction of blood eosinophilia, reduction of active inflammation, suppression of the immune response, and treatment of disease-specific and/or treatment-related complications. SoC therapy for patients with HES includes oral corticosteroids (OCS) as first-line therapy for FIP1L1-PDGFRα fusion tyrosine kinase gene translocation (F/P) negative or F/P positive HES with cardiac involvement at diagnosis, and cytotoxics (e.g., hydroxyurea) or immunomodulators (e.g., interferon alpha [INFα], cyclosporine, immunoglobulin) as second-line agents [Klion, 2009]. F/P fusion gene results in constitutive activation of tyrosine kinase, which causes aberrant eosinophil development [Reiter, 2017]. Imatinib is used as first-line therapy for F/P positive HES in adults, but it is not approved for children or adolescents.

The initial response to OCS treatment is often positive; however, long-term use is associated with significant and commonly reported adverse effects in chronic inflammatory conditions [Poetker, 2010]. This is particularly important in paediatric patients who likely have long-term sequelae. Commonly reported adverse effects in children are weight gain, growth retardation, and Cushingoid features, while increased susceptibility to infection was the most serious adverse drug reaction [Aljebab, 2017]. Therefore, with chronic use, the toxicities of OCS therapy diminish patient adherence to treatment, which may increase the risk of worsening symptoms and/or increased blood eosinophils [Roufosse, 2013].

As described herein, due to the significant tolerability issues related to long-term use of corticosteroids and other chemotherapeutics, new alternative therapies with a positive risk/benefit profile are needed.

2.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with SB-240563 can be found in the investigator's brochure (IB). Table 2 and the following section outlines the risk assessment and mitigation strategy for this protocol.

2.3.1. Risk Assessment

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Mepolizumab		
Risk of systemic reactions (Allergic [type I hypersensitivity] and Other systemic), including Anaphylaxis	• Acute and delayed systemic reactions, including hypersensitivity reactions (e.g., anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occurred within hours of administration, but in some instances had a delayed onset (i.e., days). • In a placebo-controlled study of HES in adolescent and adult participants no systemic allergic/type I hypersensitivity reactions were reported. A systemic (other) reaction was reported for 1 participant on mepolizumab; a non-serious event of rash generalised (symptom: multifocal skin reaction). The event was of mild intensity and considered resolved in 2 hours. Study treatment was continued unchanged. One participant in the placebo group and no participants in the mepolizumab group reported an anaphylaxis event. • Systemic reactions reported to date across the mepolizumab program are summarised 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 SAEs by the study Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK study team and/or GSK safety review team. • Customised AE and SAE case report forms (eCRFs) utilised for targeted collection of systemic reactions data. • Utilisation 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. • Participants are monitored in clinic for 1 hour for the first 3 administrations following dosing with mepolizumab, then follow monitoring policies for the centre. • In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there must be personnel/staff at home or in clinic who are appropriately trained in basic life support to manage the patient including administration of medications (e.g., epinephrine),

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.
Risk of local injection site reactions	• In a placebo-controlled study of severe HES in adolescent and adult participants the incidence of local injection site reactions observed with SC administration of mepolizumab was 6% (4 participants) compared with 4% (2 participants) with placebo. All events were non-serious, of mild intensity, resolved, and did not lead to study treatment discontinuation. • Local injection site reactions reported to date across the mepolizumab program are summarised in the Adverse Events of Special Interest' section of the IB; see also 'Section 6 titled 'Summary of Data and Guidance for the Investigator'.	• Daily monitoring of SAEs by the study Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK study team and/or GSK safety review team. • Customised AE and SAE eCRFs will be utilised for targeted collection of local injection site reactions data.
Potential risk of immunogenicity	• Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralising antibodies (NAb), which have the potential to modulate pharmacokinetics (PK), pharmacodynamics (PD) or produce adverse reactions. However, humanised and fully human antibodies are less immunogenic than mouse or chimeric monoclonal antibodies. • In a placebo-controlled study of severe HES in adolescent and adult participants, the incidence of immunogenicity following mepolizumab administration was low. ADA were seen in 1 (2%) participant at baseline and 1 (2%) participant at Week 32. Both participants were in the mepolizumab treatment group and had low titre values and unremarkable AE profiles. Immunogenicity data reported to date across the mepolizumab development program are summarised in the IB; see Section 5.4, 'Clinical Immunogenicity' and a summary of immunogenicity findings in the 'Other Potentially Clinically Relevant Information for the Investigator' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	• To characterise the potential risk of immunogenicity, blood samples are collected in clinical studies for detection of ADA and NAb.

2.3.2. Benefit Assessment

Study 215360 is a 52-week, open-label, single arm, multicentre study to investigate the efficacy and safety of mepolizumab SC in the treatment of HES in participants aged 6 to 17 years receiving SoC therapy.

Data from 4 completed studies have demonstrated the beneficial use of mepolizumab in participants with HES (MHE100185 [Rothenberg, 2008], MHE100901 [Roufosse, 2013], 200622 [Roufosse, 2020], and CCI [redacted] Furthermore, mepolizumab has also demonstrated clinical benefit in clinical trials in other conditions where eosinophilia is considered to play an important part in the pathology, e.g., severe eosinophilic asthma, EGPA and CRSwNP.

Data obtained from Study 215360 will provide a clinical evaluation of the efficacy and safety of mepolizumab in the treatment of paediatric HES. It is planned to use the study results and supporting data as the basis for European Medicines Agency (EMA) regulatory submissions for mepolizumab for the treatment of paediatric HES.

2.3.3. Overall Benefit: Risk Conclusion

Data from mepolizumab preclinical and clinical development support the ability of mepolizumab to inhibit IL-5, and consequently treat conditions associated with eosinophilia, such as HES. To date, the safety profile of mepolizumab has been favourable. In addition, a positive benefit/risk profile of mepolizumab in HES was shown in Study 200622 and Study 205203. There are no known safety concerns with mepolizumab to date that would preclude investigation in paediatric participants with HES. The sponsor therefore maintains that investigation of the efficacy and safety of mepolizumab is justified in Study 215360.

3. OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years with HES	• Frequency of HES flares over the 52-week study treatment period
Secondary	
• To assess the effect of mepolizumab SC given every 4 weeks on the change in OCS dose in participants aged 6 to 17 years with HES that are taking OCS at baseline	• Change in the mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 to Weeks 48 to 52 • Reduction of ≥50% in mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52 • Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52
• To assess the effect of mepolizumab SC given every 4 weeks on the change in OCS dose in participants aged 6 to 17 years with HES	• Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52
• To assess the efficacy of mepolizumab SC given every 4 weeks on fatigue in participants aged 12 to 17 years with HES	• Change from baseline in fatigue severity based on weekly average score of BFI item 3 (worst level of fatigue during past 24 hours) for Week 52
• To evaluate the immunogenicity of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years with HES	• Occurrence of ADA and NAb
• To assess the effect of long-term use of mepolizumab SC on a PD marker in participants aged 6 to 17 years with HES.	• Ratio to baseline in absolute blood eosinophil count at discrete time points during the 52-week study treatment period
• To assess the PK of mepolizumab SC in participants aged 6 to 17 years with HES	• Mepolizumab plasma concentration at discrete time points during the 52-week study treatment period

Objectives	Endpoints
Other	
CCI [redacted]	
• To evaluate the safety of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years with HES	• Occurrence of AEs and SAEs • Change from baseline in vital signs (blood pressure, heart rate, and temperature) • Change from baseline in 12-lead ECG • Haematological and clinical laboratory tests

Abbreviations: ADA, anti-drug antibody; AE, adverse event; BFI, Brief Fatigue Inventory; ECG, electrocardiogram; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; CCI [redacted] HES, hypereosinophilic syndrome; LVEF, left ventricular ejection fraction; Nab, neutralising antibodies; OCS, oral glucocorticosteroids; PD, pharmacodynamics; PK, pharmacokinetics; CCI [redacted].

Primary estimand

The primary clinical question of interest is: What is the rate of HES flares during 52 weeks of mepolizumab SC given every 4 weeks in participants aged 6 to 17 years, regardless of treatment discontinuation for any reason and regardless of changes in background therapy?

The estimand is described by the following attributes:

- Population: participants with HES aged 6 to 17 years with or without maintenance SoC therapy
- Treatment condition: Mepolizumab given every 4 weeks in addition to SoC
- Variable/endpoint: frequency of HES flares over 52 weeks
- Summary measure: annualised rate of HES flares
- Intercurrent events:
  - Study treatment discontinuation – treatment policy strategy
  - Change in background HES medication (other than changes due to a clinically documented flare) - treatment policy strategy
- Rationale for estimand:
  - Interest lies in the rate of flares when medication is taken for the entire study duration. For participants discontinuing study medication or changing background medication, use of a treatment policy strategy recognises that this could be due to an unfavourable cause.

Secondary efficacy estimands

Secondary efficacy estimands address changes in OCS use and effects on fatigue severity.

Estimands for changes in OCS use will use the subpopulation of participants with HES aged 6 to 17 years who are taking OCS at baseline. Treatment condition will be the same as for the primary estimand. The following 3 endpoints and summary measures will be used:

1. Endpoint: Change in the mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 to Weeks 48 to 52; summary measure: mean across participants.
2. Endpoint: Reduction of ≥50% in mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52; summary measure: proportion of participants with this reduction.
3. Endpoint: Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52; summary measure: proportion of participants with this level of OCS usage.

For the intercurrent event of study treatment discontinuation, a treatment policy strategy will be used. Use of OCS is part of the endpoint (composite strategy). Other changes in background HES medication will use a treatment policy strategy.

An additional estimand for changes in OCS use will use the whole population of participants with HES aged 6 to 17 years. Treatment condition will be the same as for the primary estimand. The following endpoint and summary measure will be used:

- Endpoint: Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52; summary measure: proportion of participants with this level of OCS usage.

For the intercurrent event of study treatment discontinuation, a treatment policy strategy will be used. Use of OCS is part of the endpoint (composite strategy). Other changes in background HES medication will use a treatment policy strategy.

The secondary estimand for fatigue severity will use the subpopulation of participants with HES aged 12 to 17 years. Treatment condition will be the same as for the primary estimand. A treatment policy strategy will be used for the intercurrent events of study treatment discontinuation and changes to background HES therapy. The endpoint will be the change from baseline in weekly average score of the BFI item 3 (worst level of fatigue during past 24 hours) for Week 52 and the summary measure will be the mean value.

4. STUDY DESIGN

4.1. Overall Design

This is a 52-week, open-label, single arm, multicentre study of mepolizumab SC in children and adolescent participants with HES receiving SoC therapy.

Participants will be aged 6 to 17 years at Screening (Visit 1) and are expected to remain in the study for 52 weeks. Approximately 15 participants who are on a stable dose of HES therapy for at least 4 weeks prior to Visit 2 will be enrolled. Participants will have a 2- to 4-week run-in period for training and compliance on the use of their eDiary to record daily assessments. Eligible participants will receive the first dose of mepolizumab at Visit 2.

All participants will need to attend a study-site visit at Screening (Visit 1), Baseline (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 24 (Visit 8), and the Week 52 exit visit (Visit 15). The other visits may be performed remotely where applicable country and local regulations allow. Home healthcare services may also be utilised to support these activities where local regulations and infrastructure allow. The last dose of mepolizumab will be given at Week 48 and the final visit of the treatment period will be at Week 52. There is a follow-up visit 8 weeks after the Week 52 visit (12 weeks after the last dose of mepolizumab). Protocol-defined eligible participants may enter an EAP, where available, immediately after completion of the 52-week study period (Section 6.6). Participants who enter the EAP will not need a study follow-up visit.

All participants will be on active treatment with mepolizumab. Investigators may adjust HES therapy (SoC) as needed from Visit 3 (4 weeks after the first dose of mepolizumab). All participants will be managed during the study according to routine medical care (i.e., participants and/or caregiver will be instructed to contact their investigator for evaluation or seek emergency care as necessary if they or their child experience worsening of symptoms as per their usual practice).

The investigators will use the CCI [redacted] to assess for the presence of a HES flare.

An Independent Data Monitoring Committee (IDMC) will be utilised during the study.

4.2. Scientific Rationale for Study Design

Single arm design

Mepolizumab 300 mg SC has been shown to be efficacious and well tolerated in adolescent and adult participants with HES in a pivotal Phase 3 Study 200622 and the OLE Study 205203. Therefore, it would be appropriate to provide an active treatment for paediatric participants without a risk of being exposed to placebo treatment. This allows observation of a flare rate in the study population, which is the primary objective of this study.

Study population

The study will enrol male and female participants aged 6 to 17 years with uncontrolled HES, defined by at least 2 HES flares within the past 12 months and a blood eosinophil count of ≥1000 cells/µL at Screening. The study population describes a group of participants considered likely to benefit from the addition of mepolizumab to existing therapy. In addition, the population is similar to that of Study 205203 to allow a comparison between the 2 studies.

Study treatment duration

The total study treatment duration is 52 weeks. To achieve the study objective, which is to evaluate potential long-term efficacy (primary) and safety (secondary) in the study population, a 52-week treatment period is deemed appropriate.

The 2- to 4-week run-in period allows for the assessment of participant (and caregiver) understanding and compliance with the daily eDiary and for establishing baseline data, and to allow adequate time for receipt of results from Screening assessments collected at Visit 1.

Definition of a HES flare for the primary endpoint

The primary endpoint is consistent with the efficacy endpoint utilised in the HES OLE Study 205203. The same definition of a HES flare is used in this study and Study 205203, defined as a 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 additional treatment. This will allow a comparison of the efficacy results between this study and Study 205203.

4.3. Justification for Dose

Consistent with the dose investigated in completed adult and adolescent Phase 3 HES studies 200622 and 205203, the mepolizumab dose proposed to be investigated in adolescents in this study is 300 mg SC administered every 4 weeks. CCI [redacted]. In Studies 200622 and 205203, observed mepolizumab plasma concentrations in adolescents were consistent with adults and within the adult range.

CCI [redacted] Building on the learnings from a paediatric study conducted in children aged 6 to 11 years with severe eosinophilic asthma (200363) that supported the approved paediatric dosing regimen in severe asthma, simulations and analysis in closed form were conducted. CCI [redacted]

4.4. End of Study Definition

The total study treatment duration is 52 weeks.

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if he/she has completed the last visit at Week 52, regardless of whether mepolizumab treatment was received during the entire study period. For participants who do not enter the expanded access program (EAP), the end of the study (EOS) will be considered the follow-up visit (visit 16). For participants who enter the EAP before the follow-up visit has occured, the end of study (EOS) will be considered Week 52 (visit 15).

5. STUDY POPULATION

The study will enrol participants aged 6 to 17 years with uncontrolled HES, defined by at least 2 HES flares within the past 12 months and a blood eosinophil count of ≥1000 cells/µL at Screening.

At least 15 participants will be enrolled and receive at least one dose of mepolizumab. C [redacted] CI [redacted]

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

5.1. Inclusion Criteria

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

Age

1. Participant must be aged 6 to 17 years inclusive, at Screening (Visit 1).

Type of Participant and Disease Characteristics

2. Participants who have been diagnosed with **HES for at least 6 months** prior to enrolment (Visit 2). HES diagnosis is based on signs or symptoms of organ involvement and/or dysfunction that can be directly related to:

   - Blood eosinophilia of >1500 eosinophils/µL on at least 2 occasions, and/or
   - Tissue eosinophilia

   documented prior to Visit 2 without a discernible non-haematological secondary cause (e.g., drug hypersensitivity, parasitic infection, human immunodeficiency virus [HIV] infection, non-haematological malignancy).

   Tissue eosinophilia is defined as a history of 1 or more of the following:

   - The percentage of eosinophils exceeds 20% of all nucleated cells in bone marrow sections
   - In the opinion of a pathologist, tissue infiltration by eosinophils is extensive (massive) when compared with the normal physiologic range, compared with other inflammatory cells, or both

- A specific stain directed against an established eosinophil granule protein (e.g., major basic protein) reveals extensive extracellular deposition of eosinophil-derived proteins indicative of local eosinophil activation [Valent, 2012].

3. A history of 2 or more HES flares within the past 12 months prior to Screening (Visit 1). Historical HES flares are defined as documented HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy. At least one HES flare within the past 12 months must not be related to a decrease in HES therapy during the 4 weeks prior to the flare.
4. Participants must have blood eosinophil count ≥1000 cells/µL present at Screening.
5. Participants must be on a stable dose of HES therapy for the 4 weeks prior to the first dose of mepolizumab (Visit 2). HES therapy includes but is not limited to OCS, immunosuppressive, and cytotoxic therapy. Participants who are not on maintenance therapy during this period are eligible if they meet other criteria.

Sex and Contraceptive/Barrier Requirements

6. Male and/or female [(according to their reproductive organs and functions assigned by chromosomal complement)] [FDA, 2016].

    - Contraception and barriers as well as pregnancy testing is required as appropriate for the age and sexual activity of paediatric participants and as required by local regulations.

A female participant is eligible to participate if she is either:

- Premenarcheal or
- Not pregnant as confirmed by a negative urine (or serum if required by local regulations) human chorionic gonadotrophin [hCG] test if of reproductive potential.

Females of childbearing potential must commit to consistent and correct use of an acceptable method of contraception (see Section 10.4, Appendix 4) for the duration of the trial and 16 weeks after the last dose of investigational product. A urine pregnancy test is required of females of childbearing potential. This test will be performed at the initial Screening (Visit 1) and will be performed at each scheduled treatment visit prior to the administration of investigational product, and during the exit visit, early withdrawal and follow-up visits (see Section 8.2.5).

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

Note: If the childbearing potential changes after start of the study (e.g., a premenarcheal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception or a male participant must use a condom. If reproductive status is questionable, additional evaluation should be considered.

Informed Consent and Assent

7. The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant's legal guardian, (as defined in Section 10.1.3) and the participant's assent, when applicable, before any study-specific activity is performed (unless a waiver of informed consent has been granted by an Institutional Review Board [IRB]/Ethics Committee [EC]). All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand.
8. The participant capable of providing signed and dated written assent signs and dates a written assent form (age appropriate) and the parent/guardian signs and dates a written informed consent form (ICF) for study participation prior to the initiation of any study-related activities. Informed consent is described in Section 10.1.3.

Other

9. A legal guardian or primary caregiver must be available to help the study-site personnel ensure follow-up; support the participant to attended assessment days according to the SoA (e.g., able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures); consistently and consecutively be available to provide information on the participant using the rating scales during the scheduled study visits; accurately and reliably dispense study intervention as directed.

A legal guardian or primary caregiver must be able to accurately maintain the child's take-home record, including items of general health

5.2. Exclusion Criteria

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

Medical Conditions

1. Life-threatening HES or life-threatening HES co-morbidities: Imminently life-threatening HES disease severity such that (a) likelihood of death is high unless the course of the disease is interrupted within 12 weeks prior to Visit 2 (b) likelihood of severe deterioration of HES is high unless immediate therapeutic intervention is provided.
2. Other concurrent medical conditions that may affect the participant's safety**:** Participants who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological, respiratory, or any other system abnormalities that are not associated with HES and are uncontrolled with standard treatment.
3. Eosinophilia of unknown significance
4. FIP1L1-PDGFRα (F/P) Status: Participants who test positive for F/P. Blood sampling is required for all participants at Screening (Visit 1) for this test unless the documented result is available.

5. Clinical diagnosis of EGPA
6. Infection:
    - Participants with chronic or ongoing active infections requiring systemic treatment, as well as participants who have experienced clinically significant infections due to viruses, bacteria, and fungi within 4 weeks prior to enrolment (Visit 2).
    - Participants with a pre-existing parasitic infestation within 6 months prior to enrolment (Visit 2).
7. Participants with a known immunodeficiency (e.g., HIV), other than that explained by the use of OCS or other therapy taken for HES.
8. Participants with documented history of any clinically significant cardiac damage prior to Screening (Visit 1) that, in the opinion of the investigator, would impact the participant's participation during the study.
9. Malignancy:
    - Participants with a history of or current lymphoma
    - Participants with current malignancy or previous history of cancer in remission for less than 12 months prior to Screening (Visit 1). Participants that had localised carcinoma (i.e., basal or squamous cell) of the skin that was resected for cure will not be excluded.
10. Participants who are not responsive to OCS based on clinical response or blood eosinophil counts.

Prior/Concomitant Therapy

11. Participants who have previously received mepolizumab in the 4 months prior to enrolment (Visit 2).
12. Participants receiving any of the following:
    - IV or SC corticosteroids in the 4-week period prior to enrolment (Visit 2).
    - Any other monoclonal antibodies within 30 days or 5 half-lives, whichever is longer, of enrolment (Visit 2).

Other investigational product/clinical study

13. 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 enrolment (Visit 2). The term "investigational" applies to any drug not approved for sale in the country in which it is being used or investigational formulations of marketed products
14. Use of candidate COVID-19 vaccines that have not received limited, accelerated, or full authorisation/approval, and are only in use as part of a clinical trial
15. Participants who are currently participating in any other interventional clinical study

Contraindications

16. Participants with any history of hypersensitivity to any monoclonal antibody (including mepolizumab).

Other Exclusions

17. 12-lead ECG finding:

For all participants:

- An abnormal ECG finding from the 12-lead ECG conducted at Visit 1 if considered to be clinically significant and would impact the participant's participation during the study based on the evaluation of the investigator.

For participants aged 6 to 11 years:

- QT interval corrected using Fridericia's formula (QTcF) > 450 msec.
- Left bundle branch block.

For participant aged 12 to 17 years:

- QTcF > 450 msec or QT interval corrected for heart rate (QTc) > 480 msec in participants with bundle branch block.

NOTE: 12-lead ECG results performed centrally or by the local 12-lead ECG machine at Screening (Visit 1) over-read by the centralised independent cardiologist must be received prior to assessing eligibility at Visit 2 by the investigator.

18. Liver abnormality/disease:

- Alanine aminotransferase (ALT) >2.5 × upper limit of normal (ULN) or ALT>5 × ULN if documented HES with liver manifestations
- Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
- Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
- Presence of hepatitis B surface antigen (HBsAg) at Screening or within 3 months prior to first dose of study intervention
- Positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study intervention

NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained.

- Positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of study intervention

NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

19. Other laboratory abnormalities:

    - Evidence of clinically significant abnormality in the haematological, biochemical, or urinalysis screen from the sample collected at Screening (Visit 1), that could put the participant's safety at risk by participating in the study, as judged by the investigator

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Method of Study Enrolment

Participants are required to meet the inclusion criteria for enrolment to treatment detailed in Section 5.1. Participants meeting exclusion criteria for enrolment to treatment will not be enrolled to treatment.

Participants will be enrolled to the single treatment arm using IVRS.

Study treatment will be dispensed at the study visits summarised in the SoA. Returned study treatment should not be re-dispensed to the participants.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 including ethnicity and race where permitted by local regulations, screen failure details, eligibility criteria, any protocol deviations, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants will be assigned a new participant number for every screening/rescreening event.

5.6. Criteria for Temporarily Delaying Enrolment /Administration of Study Intervention Administration

There is no reason for enrolment to be delayed in this study when inclusion/exclusion criteria are met.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

Mepolizumab will be administered to the participant by a trained healthcare provider (HCP). The study intervention is described in Table 4.

Table 4 Study Investigational Product

Arm Name	Mepolizumab
Intervention Name	SB240563 (mepolizumab)
Type	Biologic
Dose Formulation	Sterile liquid formulation
Unit Dose Strength(s)	CCI [redacted]
Dosage Level(s)	
Route of Administration	SC injection. Injections should be administered into the upper arm or thigh.
Sourcing	Provided centrally by the sponsor.
Packaging and Labelling	Study intervention will be provided in pre-filled safety syringe. Each pre-filled safety syringe will be labelled as required per country requirement. The contents of the label will be in accordance with all applicable regulatory requirements.

Mepolizumab (SB-240563) is a humanised IgG monoclonal antibody (IgG1, kappa) with human heavy and light chain frameworks. CCI [redacted]

All participants will receive active treatment with mepolizumab SC injection every 4 weeks over a treatment period of 52 weeks (the last dose at 48 weeks). CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

CCI [redacted]. Posology for multiple injections states each injection should be administered at least 5 cm apart.

In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there must be personnel/staff at home or on site at the treatment facility who are appropriately trained in basic life support to manage the patient including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to a facility for additional care if appropriate. Participants are monitored in clinic for 1 hour for the first 3 administrations following dosing, then follow monitoring policies for the centre. Epinephrine is required to be available on site or at home for each enrolled participant during each administration of mepolizumab.

6.1.1. Medical Devices

The GSK manufactured medical devices provided for use in this study are pre-filled safety syringes.

Instructions for medical device use are provided in the instructions for use in the study reference manual (SRM) to the investigators and HCPs administering the intervention.

All device deficiencies, (including malfunction, use error, and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 8.3.8) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability of Study Intervention

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all mepolizumab received and any discrepancies are reported and resolved before use of mepolizumab.

Only participants enrolled in the study may receive mepolizumab and only authorised HCPs may supply or administer mepolizumab in accordance with the protocol. Mepolizumab must be stored in a secure, environmentally controlled storage or refrigerator at a temperature of 2 to 8°C, protected from light, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff. Maintenance of a temperature log (manual or automated) is required.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention are provided in the SRM.

Under normal conditions of handling and administration, mepolizumab is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure, notify the monitor, Medical Monitor and/or GSK study contact.

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

The excipients used in the paediatric formulation are safe for administration in the paediatric population participating in the study.

6.3. Measures to Minimise Bias: Randomisation and Blinding

This is an open-label single-arm study. All screened participants will be identified by a unique participant number that will remain consistent for the duration of the study. Upon completion of all the required screening assessments, eligible participants will be registered into the study by the investigator or authorised site staff.

6.4. Study Intervention Compliance

When participants are dosed at home or at the site, they will receive study intervention directly from the investigator, a designee, or a home study nurse, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

6.5. Dose Modification

CCI [redacted]

Table 5 Dose Modification Recommendations

CCI [redacted]

6.6. Continued Access to Study Intervention After the End of the Study

Eligible participants may enter an EAP, where available. The first EAP dose may occur before the follow-up visit, after completion of the 52-week study period. In this case, participants will not require a follow-up visit.

Participants who discontinue the study treatment but continue in the study per protocol (including HES flare-related assessments) until 52 weeks from study entry will be considered for the EAP, but participants who withdraw from the study prematurely will not be considered for an EAP.

Study procedures for the EAP are described separately.

6.7. 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 judgement in treating the symptoms of a suspected overdose and record the overdose in the electronic case report form (eCRF).

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 study Medical Monitor immediately.

6.8. Concomitant Therapy

Participants will be permitted to continue their SoC HES therapy (concomitant therapy) throughout the study period. Starting at 4 weeks after the first dose of mepolizumab (Visit 3), investigators may adjust SoC doses as medically appropriate based on clinical symptoms and blood eosinophil counts.

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

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

Any investigational agents (biologic or non-biologic) are not allowed within the 30 days or 5 drug half-lives, whichever is longer, prior to Screening (Visit 1), and until Visit 15. The term "investigational" applies to any drug not approved for sale in the country in which it is being used or investigational formulations of marketed products. Anti-IL-5 and anti-IL-5-receptor therapies are not permitted to be used during the study (from Visit 1 until the end of study visit, See Section 4.4), whether investigational or non-investigational.

For participants who are required to complete the follow-up visit, prohibited medications, such as anti-IL-5 / IL-5 receptor therapy, must not be started until the follow-up visit is complete. The follow-up period is required to reflect the safety information after 12 weeks from the last IP dose.

In general, GSK study participants can be vaccinated against COVID-19 using vaccines authorised via limited regulatory mechanisms (e.g., Emergency Use Authorisation [EUA]) or approved via accelerated or full approval mechanisms.

Use of other candidate COVID-19 vaccines that have not received limited, accelerated, or full authorisation/approval, and are only in use as part of a clinical trial, are not allowed.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants who discontinue study treatment prematurely, where possible, continue in the study per protocol until 52 weeks after the first dose of mepolizumab in Study 215360 (Visit 15), including the collection of biological samples for laboratory assessments approximately 4 weeks and 12 weeks after the last dose of study treatment as well as daily eDiary completion. Reasons for premature discontinuation of study treatment must be captured in the CRF, e.g., AE, lack of efficacy, protocol deviation, pregnancy, investigator discretion, lost to follow-up, study termination.

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

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

- Pregnancy
- Meets liver chemistry stopping criteria (Section 7.1.1)
- Meets QTc stopping criteria (Section 7.1.2)

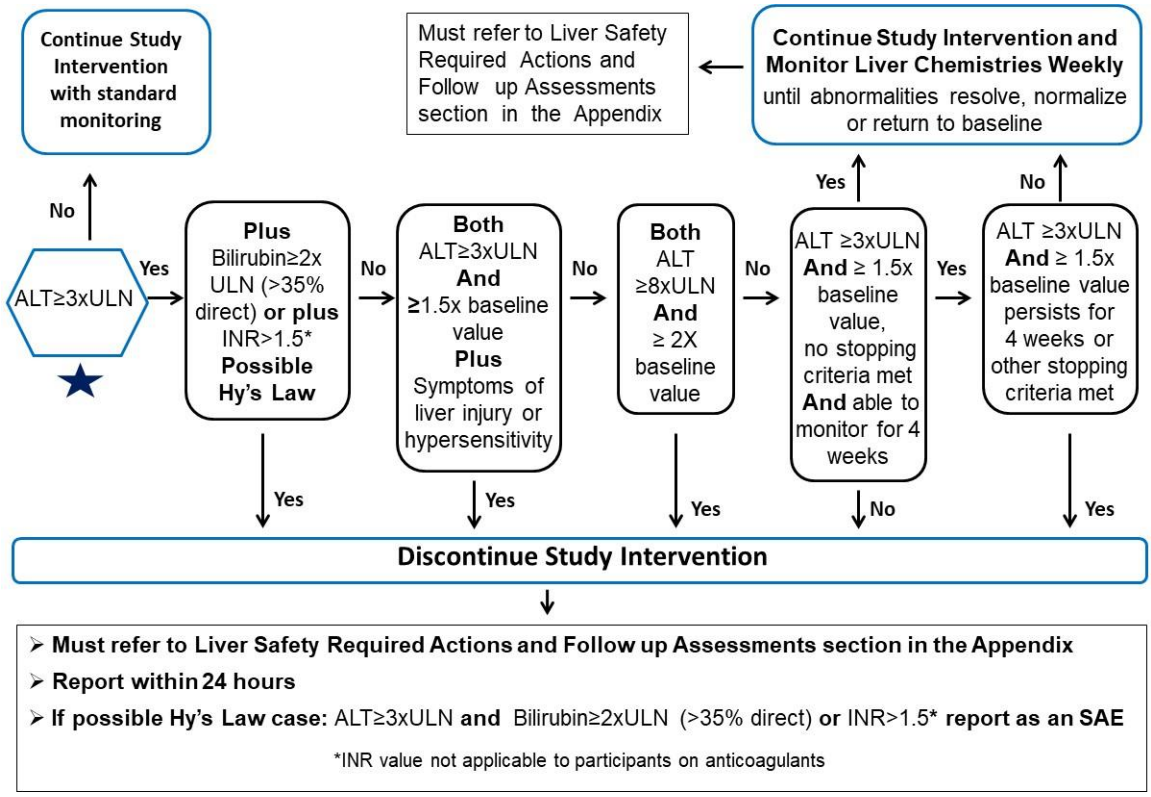
7.1.1. Liver Chemistry Stopping Criteria

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

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

- a participant meets 1 of the conditions outlined below, or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

Figure 2 Liver Stopping and Monitoring Event Algorithm



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

Refer to Appendix 5 for required Liver Safety Actions and Follow-up Assessments.

7.1.2. QTc Stopping Criteria

For trial eligibility and discontinuation, the same QTcF correction formula will be used for *all* participants in this trial. A participant who meets either bulleted criteria below based on the average of triplicate ECG readings will be discontinued from study intervention:

For participants aged 6 to 11 years:

- QTcF > 480 msec (corrected QT only)

For participants aged 12 to 17 years:

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

For all participants with underlying bundle branch block, follow the discontinuation criteria listed below in Table 6:

Table 6 QTc Stopping Criteria

Baseline QTcF with Bundle Branch Block	Discontinuation QTcF with Bundle Branch Block
< 450 msec	> 500 msec
450 to 480 msec	> 530 msec

Abbreviations: QTc, corrected QT interval; QTcF, corrected QT interval Fridericia's formula.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcF) after enrolment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Temporary Discontinuation

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

7.1.4. Rechallenge

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

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

7.2. Participant Discontinuation/Withdrawal from the Study

The legal guardian and the paediatric participant have the right to withdraw permission (consent or assent, respectively) at any time during the study. If the study staff identify any reluctance in the legal guardian or paediatric participant (e.g., signs of verbal or physical dissent) about continued participation in the study, the paediatric participant's continuation in the study should be re-evaluated. The same principles that govern permission/assent/consent also govern its withdrawal.

At the time of withdrawal from the study, if possible, a withdrawal visit should be conducted, as shown in the SoA.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- The primary reason(s) for participant discontinuation/ withdrawal from the study will be documented in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved.

Investigators will attempt to contact participants or parent(s)/guardian(s) who do not return for scheduled visits or follow-up.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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 and/or caregiver (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.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.10.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

Protocol waivers or exemptions are not allowed.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments (at the discretion of the investigator). The site may work with GSK to use a centrally appointed home nursing vendor for conduct of study assessments.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

The maximum amount of blood collected from each participant over the duration of the study, excluding extra assessments will not exceed 97 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Samples for eosinophil counts at screening V1 only, may be analysed by a local lab if required. Local lab eosinophil count results will be entered to the eCRF. Samples will also be sent for central testing, with the higher of the cell count values to be used to fulfil the entry criteria for enrolment.

Demographic data related to sex, race and ethnicity will be collected at V1 and is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

Participant's medical/vaccination history will be obtained by interviewing the participant or their parent/caregiver and/or review of the participant's medical records. Any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention will be recorded in the eCRF.

8.1. Efficacy Assessments

An eDiary will be used to electronically collect a number of patient-reported outcomes (PROs) as described in this section. All participants will receive sufficient training on PRO completion using electronic devices. Registration and training for the eDiary is covered in the SRM.

Planned time points for all efficacy assessments are listed in the SoA (Section 1.3).

8.1.1. HES Flare

A HES flare is defined as a 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 10 mg/day for 5 days
- An increase in or addition of any immunosuppressive and/or cytotoxic HES therapy from/to the most recent dose of HES therapy.

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

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

When a participant experiences a 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 participant'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 a HES flare between scheduled clinic visits, when possible, the participant 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 participant via telephone and complete the CCI [redacted] If an escalation of therapy is initiated by a non-study physician, the investigator should confirm that the escalation in therapy is attributable to a HES-related clinical manifestation.

CCI [redacted]

8.1.3. Reduction of Use of OCS, Immunosuppressive and/or Cytotoxic HES Therapy

Reduction of use of OCS, immunosuppressive and/or cytotoxic HES therapy will be considered efficacy assessments as aligned with endpoints in this study, namely:

- Change in the mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 to Weeks 48 to 52 in participants that are taking OCS at baseline
- Reduction of ≥50% in their mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52 in participants that are taking OCS at baseline
- Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52 in participants that are taking OCS at baseline
- Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52
- CCI [redacted]

[redacted]

CCI [redacted]

CCI

[redacted]

8.1.5. Brief Fatigue Inventory item 3

Change from baseline in fatigue severity will be measured based on the weekly average score of the BFI item 3 (worst level of fatigue during past 24 hours) for Week 52 in participants aged ≥12 years.

Item 3 of the BFI is an 11-point scale that measures fatigue (weariness, tiredness) ranging from 0 “no fatigue” to 10 “as bad as you can imagine” (Section 10.9).

CCI

[redacted]

CCI

8.2. Safety Assessments

Planned time points for all safety assessments are listed in the SoA (Section 1.3). Additional time points for safety tests (such as vital signs, physical exams, and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

8.2.1. Physical Examinations

Height and weight will be measured using a calibrated stadiometer (appropriate for the participant's age) and plotted on age and gender appropriate charts so that a visual assessment can be performed relative to normative standards for height and weight and change in height and weight over time (Section 10.13).

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

8.2.2. Vital Signs

Vital signs will include temperature, systolic and diastolic blood pressure, and heart rate.

Blood pressure and pulse measurements will be assessed with a completely automated device using an appropriate size cuff in a sitting position. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.2.3. Electrocardiograms

12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

If prolonged QT/QTcF is noted, 2 additional ECGs measurements should be obtained. Determination of whether eligibility or discontinuation criteria are met will be based on the average of the triplicate assessment.

8.2.4. Clinical Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, 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 intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or study Medical Monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

If laboratory values from non-protocol-specified laboratory tests 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 eCRF.

8.2.5. Pregnancy Testing

Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.

Pregnancy testing (urine or serum as required by local regulations) should be conducted prior to each dose of study intervention during study intervention period.

Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure (at the follow-up visit).

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

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs or SAEs can be found in Section 10.3.

The definitions of device-related safety events, (adverse device effects [ADEs] and serious adverse device effects [SADEs]), can be found in Section 10.6. Device deficiencies are covered in Section 10.6.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

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

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1. Time Period and Frequency for Collecting Adverse Events and Serious Adverse Event Information

All SAEs will be collected from the start of study intervention until the follow-up visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

Clinical Presentation of Adverse Events

Study-site staff should instruct the legal guardians and caregivers, on how to report signs and symptoms (e.g., crying and pain) in the individual paediatric participant. They will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhoea, sleepiness, variation in the intensity and pattern of crying, etc.). These non-specific symptoms may be the only manifestations of some adverse reaction observed in children aged 6 to 11 years. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

These events may or may not have been noted in the participant diary.

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

8.3.3. Follow up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.7), will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

For [SAEs], the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Ethics Committees (EC), and investigators.

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

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

8.3.5. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 16 weeks after the last dose of study intervention.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant's pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. 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 in the study will discontinue study intervention.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV eCRFs 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 eCRF within 1 week of receipt of a CV event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

8.3.7. Adverse Events of Special Interest

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

1. Systemic reactions
2. Local injection site reactions

In addition, the information as to whether an event met the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] (Appendix 7) will be collected on the AE and SAE eCRF pages.

8.3.8. Medical Device Deficiencies

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

If the site(s) uses non-sponsor medical devices, i.e., medical devices not provided by GSK, then the investigators are obligated to report any device deficiencies to the legal manufacturer of the devices directly

The definition of a medical device deficiency can be found in Section 10.6.3.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.3 of the protocol.

8.3.8.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a device deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

Medical device deficiencies and any associated AE/SAEs for associated person (i.e., spouse, caregiver, site staff) will be collected. The associated person will be provided with a Safety reporting information and authorisation letter.

The method of documenting medical device deficiencies is provided in Section 10.6.

8.3.8.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention or the study, and associated persons.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.8.3. Prompt Reporting of Medical Device Deficiencies to the Sponsor

Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.

The medical device deficiency report form will be sent to the sponsor by email.

The sponsor will be the contact for the receipt of device deficiency reports.

8.3.8.4. Regulatory Reporting Requirements for Medical Device Incidents

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

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

8.4. Pharmacokinetics

Blood samples for determination of mepolizumab plasma concentration will be collected prior to dosing at the time points indicated in the SoA (Section 1.3). The actual date and time of each blood sample collection will be recorded.

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

8.5. Pharmacodynamics

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

Blood samples will be collected for measurement of total serum IL-5 levels at the visits specified in the SoA (Section 1.3).

Blood samples will be collected to measure total IgE, according to the SoA (Section 1.3).

8.6. Immunogenicity Assessments

Immunogenicity will be assessed in this study by measuring ADA and NAb. Blood samples will be collected prior to dosing at visits specified in the SoA. Under supervision of the sponsor, samples will be analysed with validated assays for the presence of ADA (screening, confirmation, and titre analysis) and for the presence of NAb (if necessary). Processing, storage, and shipping procedures are provided in the SRM.

8.7. T-cell Profile

Patients with lymphoproliferative HES or those with an abnormal T-cell phenotype are at an increased risk of developing T-cell lymphoma as part of the natural history of the disease. CCI [redacted]

Participants with a history of or current lymphoma, malignancy, or previous history of cancer in remission for less than 12 months prior to enrolment will be excluded from the study. A blood sample will be collected at Screening (Visit 1) to evaluate the T-cell profile. In addition, sites may use a documented T-cell profile result, if available, to rule out lymphoma and to determine the eligibility for participation in the study.

The T-cell profile sample (collected at visit 1 screening) is required per protocol. However, please note that the result of the T-cell profile sample (collected at visit 1 screening) is required for inclusion/exclusion determination at visit 2 (enrolment/randomization) only if the investigator requires the result as part of their clinical diagnosis, or the investigator cannot determine the risk of lymphoma using other clinical measures, such as medical history and complete blood count with differential.

8.8. F/P Status

The FIP1L1-PDGFRα fusion tyrosine kinase gene translocation (F/P) is a consequence of an interstitial chromosomal deletion [Cools, 2003] and detected in a subset of patients with HES.

A blood sample will be collected at Screening (Visit 1) to determine the F/P status for every participant unless the documented result is available. Participants who are F/P positive are excluded from this study.

8.9. Genetics

Optional genetics analysis sub-study will not be conducted in this study.

8.10. Biomarker

Optional biomarkers analysis sub-study will not be conducted in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary endpoint in this study is the frequency of HES flares over the 52-week study treatment period. No formal statistical hypotheses will be tested.

9.2. Sample Size Determination

At least 15 participants aged 6 to 17 years will be enrolled. Due to the rare nature of HES in paediatrics, there is minimal data available to predict the age distribution in the study. CCI [redacted]

Sample size was chosen based on the expected precision of the estimate. No sample size reassessment is planned.

Expected Precision of Estimate

The expected variance in annualised flare rate has been estimated based on the data from the completed Study 205203, which used the same definition of HES flare. In that study, flare rate was estimated using the negative binomial model with the standard error (SE) expressed on the log scale, therefore the uncertainty around the expected point estimates of effect is presented in terms of 95% confidence intervals (CIs) rather than by the variance.

Table 7 presents estimated 95% CIs for differing values of the observed mean flare rate/year.

The observed flare rate in Study 205203 was 0.26/year. If the same rate was observed in this study with 15 participants, the 95% CI would be (0.07, 0.93).

Table 7 Estimated Precision by Observed Mean Flare Rate/Year for Sample Size of 15

Observed mean flare rate/year	Approximate 95% CI for observed mean flare rate/year* with N=15
CCI [redacted]	

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set	The full analysis set will include all participants that have received at least 1 dose of mepolizumab. This will constitute the primary population for all analyses of efficacy and safety measures.

9.4. Statistical Analyses

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Primary Endpoint

The primary endpoint and estimands are described in Section 3.

The primary endpoint (variable) for this study is the frequency of HES flares during the treatment period. To be considered as a separate episode of HES flare, the start date of a HES flare must be at least 14 days apart from the resolution date of the preceding HES flare. The summary measure will be the mean flare rate per year. A treatment policy strategy will be used for the intercurrent events of discontinuation of study medication and change in background HES medication (other than changes due to a clinically documented flare).

The study is designed to collect data on HES flares for participants who discontinue from treatment. All data on HES flares collected for these participants will be included in the primary analysis. Missing data is expected to be minimal. For participants withdrawing prematurely from the study during the 52-week treatment period, all data up to the time of study withdrawal will be used to calculate the rate of HES flares. A sensitivity analysis to assess the impact of missing data may be performed; if there is sufficient off-treatment data (i.e., data collected following treatment discontinuation prior to study withdrawal) a multiple imputation approach will be used using this off-treatment data to impute missing data.

The annualised rate of HES flares will be estimated using a negative binomial generalised linear model with a log-link function, including terms for baseline OCS dose, region, age (6 to 11 years or 12 to 17 years), and observed time (as an offset variable).

The flare rate will be summarised for all participants in the study and separately for participants aged 6 to 11 years and aged 12 to 17 years.

9.4.2. Secondary Efficacy Endpoints

The secondary endpoints and estimands are described in Section 3. Estimands for changes in OCS use will use the subpopulation of participants with HES aged 6 to 17 years that are taking OCS at baseline. An additional estimand for changes in OCS use will use the whole population of participants with HES aged 6 to 17 years. The secondary estimand for fatigue severity will use the subpopulation of participants with HES aged 12 to 17 years.

All secondary efficacy endpoints will be summarised descriptively. For the estimands for changes in OCS use, a treatment policy strategy will be used for the intercurrent events of discontinuation of study medication. For these estimands, use of OCS is part of the endpoint (composite strategy). Other changes in background HES medication will use a treatment policy strategy. For the secondary estimand for fatigue severity a treatment policy strategy will be used for the intercurrent events of discontinuation of study medication and change in background HES medication.

For the following dichotomous secondary endpoints, participants withdrawing prematurely from the study who have no available data during Weeks 48 to 52 will be summarised as not having met the endpoint criteria i.e., a treatment failure:

- Reduction of ≥50% in mean daily OCS dose (prednisone/prednisolone or equivalent) from Weeks 0 to 4 compared with Weeks 48 to 52 in participants that are taking OCS at baseline
- Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52 in participants that are taking OCS at baseline
- Achieving a mean daily OCS dose (prednisone/prednisolone or equivalent) of ≤7.5 mg during Weeks 48 to 52

For all other secondary endpoints, available data up to the time of study withdrawal will be summarised.

CCI

9.4.4. Safety Analysis

AEs will be coded using the MedDRA coding dictionary and summarised by preferred term. SAEs pre-treatment and AEs and SAEs on-treatment and post-treatment will be summarised separately. Separate summaries will be provided for all AEs, drug-related AEs, SAEs, events of special interest and for AEs leading to permanent discontinuation of mepolizumab treatment or withdrawal from the study.

Immunogenicity data, ECG, vital signs, and laboratory data will be summarised descriptively.

9.4.5. Pharmacokinetic and Pharmacodynamic Analyses

Ratio to baseline in absolute blood eosinophil count will be summarised descriptively.

PK and PK/PD (blood eosinophils) data will be analysed by population methods using non-linear mixed effects modelling. Further details will be provided in the Statistical Analysis Plan (SAP).

Plasma concentration data will be summarised and displayed in both tabular and graphical form. Depending on the data, results will be analysed using WinNonlin and/or modelled using validated software such as the computer program NONMEM. Details of the PK analyses will be provided in the SAP.

Analyses will also be performed to determine any potential relationships between plasma concentrations of mepolizumab, blood eosinophils counts, and other clinical and/or exploratory endpoints. If appropriate PK and PD data from all participants will be pooled and analysed using a population approach. Population and individual post hoc estimates will be derived for key PK parameters of interest. Further details of the PK and PK/PD analyses will be provided in the report and SAP.

9.5. Interim Analysis

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Regulation [EU] No 536/2014 (Regulation [EU] No 536/2014 Annex I, section D, no. 17, letter am.)
- Applicable laws and regulations

- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/ Ethics Committee (EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.
- Any amendments to the protocol will require EC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/EC of serious adverse events (SAE) or other significant safety findings as required by IRB/EC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), International Conference for Harmonisation (ICH) guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

The investigator will be responsible for reporting cases of suspected child abuse and/or neglect according to local medical association (e.g., American Academy of Pediatrics [AAP], European Union Academy of Paediatrics) or Health Department guidelines.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent and Assent Process

Legal Guardian Consent and Paediatric Participant Assent Processes:

- The investigator, or a person designated by the investigator, will provide the legal guardian with the written ICF and the participant with the assent if applicable and explain the nature of the study, including the study risk and benefits. Participants must be informed that participation is voluntary. The legal guardian will be required to sign written consent, and the participant if applicable will be required to sign written assent, that meets the requirements of 21 CFR 50, local regulations, International Conference on Harmonisation (ICH) guidelines privacy and data protect requirements, where applicable, and the IRB/EC or study centre after the nature of the study has been fully explained and before performance of any study-related activity.
- Sample testing will be done in accordance with the recorded consent of the individual [participant/participant's parent(s)/LAR(s)].
- By default, collected samples for the study will be stored for a maximum of 20 years. This storage period begins when the last participant completes the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.
- Assent requirements for paediatric participants may vary across regions and countries; local regulations should be followed as appropriate.
- The medical record must include a statement that written informed consent from the legal guardian and assent from the paediatric participant (if deemed appropriate by local ethics review or local regulations) were obtained before the participant was enrolled in the study and the date the written consent and assent were obtained. The medical record should describe how the clinical investigator determined that the person signing the ICF was the participant's legal guardian. The authorised person obtaining the informed consent must also sign the ICF and assent form attesting that the paediatric participant did not show signs of dissent particularly in those studies including toddlers and small children; it should be written in language appropriate to the child's developmental and functional status.
- Participants and their legal guardian must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.

- Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their legal guardian still wants them to participate.
- Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.
- A copy of the informed consent and assent forms must be provided to the participant and the participant's legal guardian.
- If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.
- As appropriate, participants may be given the opportunity to meet privately with a member of the site staff to ask confidential questions and to decline assent for confidential reasons, which, at their request, would not be shared with their legal guardian, unless required by local law.
- Stored samples will be coded throughout the sample storage and analysis process and will not be labelled with personal identifiers. Participants may withdraw their consent/assent for their samples to be stored for research.

10.1.4. Recruitment Strategy

- The study is planned to be conducted at sites in multiple countries. A Patient Engagement Plan provides details of strategies to recruit and retain patients in the study, to be applied at site and community outreach (e.g. Advocacy group) levels. There are no site-specific recruitment plans. Recruitment will be tracked using RAMOS NG system.
- The Patient Engagement Plan may be adapted based on the actual number of participants enrolled in each country.
- CCI [redacted]
- The procedures for participants identification/recruitment (e.g., referral letters, advertisements etc.) must be approved by the IRB/IEC together with the material intended for participants identification/recruitment and participants use.

10.1.5. 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 that would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.

- The participant and legal guardian 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 who will be required to give consent for his/her data to be used as described in the informed consent.
- The participant and legal guardian must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.6. Committees Structure

10.1.6.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) with external experts experienced in treating paediatric patients with hypereosinophilic syndrome (HES) will be utilised to ensure external objective review of the safety data at regular intervals throughout the study.

Details of the structure and function of the IDMC, and analysis plan for IDMC reviews, are outlined in the IDMC Charter.

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 6 months of primary/study completion date (pediatric population) and within 12 months of primary/ study completion date (adult population). Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the layperson summary of results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants' received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymised patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-

identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on a printed or electronic case report form (CRF) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.Guidance on completion of CRFs will be provided in the CRF Guidelines.Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan or equivalent Contract Research Organisations (CRO) document.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for a minimum period of 15 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. In the event of a conflict between this Protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.
- When source data are sent for external assessment or adjudication (e.g., endpoint adjudication committee; expert reader), source data are stored by the external body for 25 years.

10.1.9. Source Documents

- For this study [there will not be] source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised 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.
- Source data are shared with third parties contracted by GSK for external assessment or adjudication (e.g. endpoint adjudication committee; expert reader). The non-exhaustive list of source data shared may include, discharge summaries, imaging reports, scans, videos, pathology reports, biological specimens, ECG reports, etc. Participant names or any information which would make the participant identifiable or is not essential for the external asessment or adjudication will be redacted by the investigator sites prior to transfer. Details of the participant information redaction strategy are provided in the relevant third party manuals and/or study plans. These source data will be used by the third party solely for the purpose indicated within this protocol.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The date First Centre Initiated will be the study start date.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator.
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the central laboratory, and, in certain cases, by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 8 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Haematology[1]	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[2, 3]	BUN	Potassium	AST/ SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/ SGPT	Total Protein
	Glucose	Calcium	Alkaline phosphatase[3]	
Routine Urinalysis[4]	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing[5]	• Highly sensitive serum or urine hCG pregnancy test (as needed for females of childbearing potential)			
Other Screening Tests	• Serology (hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • All study-required laboratory tests will be performed by a central laboratory, with the exception of parasitic screening, urinalysis and urine pregnancy tests. o Parasitic Screening is only required in regions with high-risk or for participants who have visited high-risk regions in the past 6 months. Sites should use local laboratories where available. If no local laboratories are available, the tests should be performed centrally. o If central laboratories are used, stool microscopy test for ova and parasites is done. The organisms detected by this test can be viewed in the SRM. It is important to note that the test provided by the central laboratory will only detect the organisms listed. If the			

Laboratory Assessments	Parameters
	participant may potentially carry any parasitic infection not covered by the central laboratory test, then the investigator is required to arrange any specialist reviews or alternative testing (using local laboratories). • PK, immunogenicity, and biomarker tests

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HBsAg, hepatitis B surface antigen; hCG, human chorionic gonadotropin; INR, international normalised ratio; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume; PK, pharmacokinetic; RBC, red blood cell; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; ULN, upper limit of normal; WBC, white blood cell.

NOTES:

1. Eosinophil count may be tested locally for screening visit 1 only. If a local sample is required, it is important that a sample for central analysis is obtained at the same time.
   Local lab eosinophil count results performed at the screening visit (visit 1) will be entered to the eCRF. If local lab samples are taken, a second sample will also be sent for central testing, with the higher of the eosinophil cell count values to be used to fulfil the entry criteria for enrolment.
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.5 All events of ALT ≥3 × upper limit of normal (ULN) and total 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).
3. If alkaline phosphatase is elevated, consider fractionating.
4. If found abnormal, the urine sample will be sent to the central laboratory for further testing.
5. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. If a test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy sample will be sent to the central laboratory for further testing.

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

10.3.1. Definition of AE

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
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 hospitalisation or prolongation of existing hospitalisation** • In general, hospitalisation signifies that the participant has been admitted (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 hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. **Results in persistent or significant disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. **Is a congenital anomaly/birth defect**
f. **Other situations:** • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgement should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

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

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- 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 required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

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: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

- 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.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the 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 1 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 recognised follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK 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 report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor or the SAE coordinator by telephone. • If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**. • 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 data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Females of Childbearing Potential (FOCBP)

Females are considered FOCBP (fertile) following menarche.

For individuals with permanent infertility due to a medical cause, investigator discretion should be applied.

10.4.2. Contraception Guidance

• **CONTRACEPTIVES[1] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[2] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[2]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[2]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) • Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[3] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

• Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[3]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[3]
  • oral
  • injectable

• Sexual abstinence   • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

1. Contraceptive use by males or females should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

2. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
3. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those that inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase 3-4 Liver Chemistry Stopping and Increased Monitoring Criteria are designed to ensure participant safety and evaluate liver event aetiology. Liver chemistry stopping criteria are shown in Table 9 and liver chemistry increased monitoring criteria are shown in Table 10.

Table 9 Liver chemistry stopping criteria

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT absolute	**Both** ALT ≥ 8 × ULN **and** ≥ 2× baseline value
ALT Increase	**Both** ALT ≥ 3 × ULN **and** ≥ 1.5 × baseline value that persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3 × ULN **and** total bilirubin ≥ 2 × ULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3 × ULN **and** INR>1.5
Cannot monitor	**Both** ALT ≥ 3 × ULN **and** ≥ 1.5 × baseline value and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	**Both** ALT ≥ 3 × ULN **and** ≥ 1.5 × baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study intervention. Report the event to GSK **within 24 hours** • Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments as described in the Follow-up Assessments column • Monitor the participant until liver chemistry levels resolve, stabilise, or return to within baseline (see **MONITORING**) **MONITORING:** **If ALT ≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participants twice weekly until liver chemistries resolve, stabilise, or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria (total bilirubin <2 × ULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within 24-72 hours • Monitor participants weekly until liver chemistries resolve, stabilise, or return to within baseline **RESTART/RECHALLENGE** **Do not restart/rechallenge participant with study intervention since not allowed per protocol; 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 aminotransferases values show a downward trend • Blood sample for PK analysis, obtained within 1 week after last dose[5] • Serum CPK, LDH, GGT, GLDH, and serum albumin • Fractionate bilirubin if total bilirubin ≥2 × ULN • Obtain complete blood count with differential to assess eosinophilia; note that the mechanism of action of mepolizumab leads to lowering of eosinophils • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications • Record alcohol use on the liver event alcohol intake form **If ALT ≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5 obtain the following in addition to the assessments listed above:** • 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 assay should be conducted (if available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. (e.g., where the

Required Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-up Assessments**
	participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation • If liver biopsy conducted complete liver biopsy form.

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRF, case report form; DILI, drug-induced liver injury; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; GSK, GlaxoSmithKline; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; INR, international normalised ratio; LDH, lactate dehydrogenase; PK, pharmacokinetics; SAE, serious adverse event; ULN, upper limit of normal.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** total 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** total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and hepatitis B core antibody (IgM); Hepatitis B DNA (will be done in certain circumstances) ; Hepatitis C RNA; Hepatitis D (delta) antibody (will be done if the patient meets liver stopping criteria or in certain circumstances); Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention 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.

Table 10 Liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3 × ULN **and** ≥ 1.5 × baseline value and not meeting any stopping criteria, without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.	• Notify the study Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin, and INR) until the values resolve, stabilise or return to within baseline levels • If at any time the participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3 × ULN and <1.5 × baseline value, and bilirubin <2 × ULN and INR ≤1.5, monitor participants twice monthly until liver chemistry values resolve or return to within baseline levels

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GSK, GlaxoSmithKline; INR, international normalised ratio; ULN, upper limit of normal.

10.6. Appendix 6: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

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

10.6.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of Medical Device SAE, SADE and USADE

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

10.6.3. Definition of Device Deficiency

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

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

AE, SAE, and Device Deficiency Recording

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

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories: Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Intensity
• Note: An event is defined as 'serious' when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, not when it is rated as severe. • Other measures to evaluate AEs and SAEs may be utilised (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

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

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

10.6.5. Reporting of SAEs

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

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the medical monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper 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 paper data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.6.6. Reporting of SADEs

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

10.6.7. Reporting of Medical Device Deficiencies for Associated Person

Reporting to GSK
If an Associated Person (i.e. spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the authorization to contact physician letter. If follow up information is required, authorization to contact physician (or other licensed medical practitioner') must be signed to obtain consent. • Medical device deficiencies that are not related to an AE or SAE should be reported via email to gsk-rd.complaints@gsk.com, using the medical device deficiency report form.

Reporting to GSK
• If the medical device deficiency is related to a non-serious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to gsk-rd.complaints@gsk.com only. • If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours, to both uk.gsk-rd-gcsp-ctsm-admin@gsk.com (or fax +44(0)20 8754 7822) and gsk-rd.complaints@gsk.com. The associated SAE form should also be reported to uk.gsk-rd-gcsp-ctsm-admin@gsk.com (or fax +44(0)20 8754 7822). • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for Medical Device Deficiency reporting can be found in the medical device deficiency report form.

10.7. Appendix 7: Anaphylaxis Criteria

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

1. Acute onset of an illness (minutes to several hrs) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus or flushing, swollen lips tongue- uvula), and at least one of the following:

- Respiratory compromise (e.g., dyspnoea, 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 hrs):

- Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (e.g., dyspnoea, 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

CCI

[redacted]

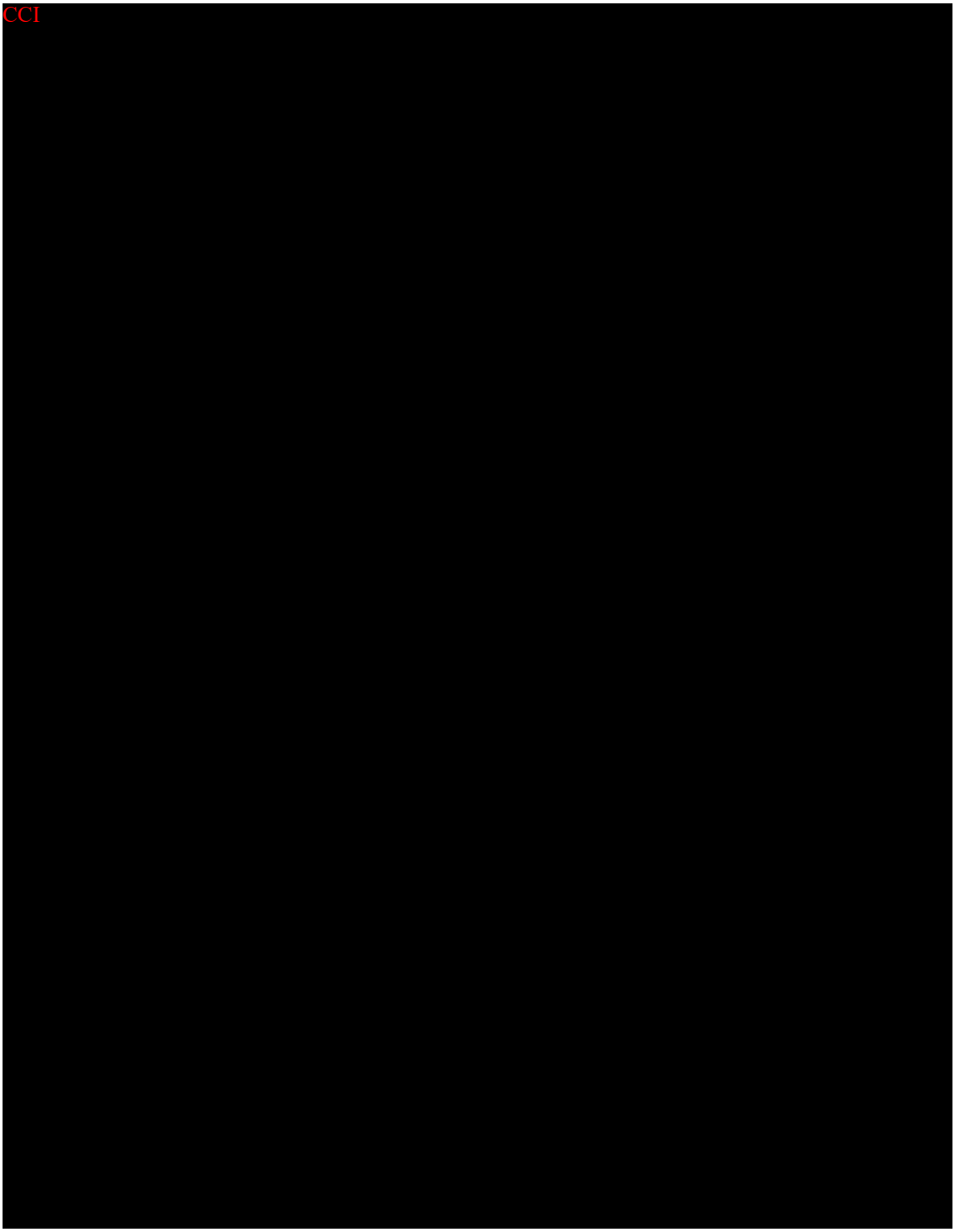
CCI

[redacted]

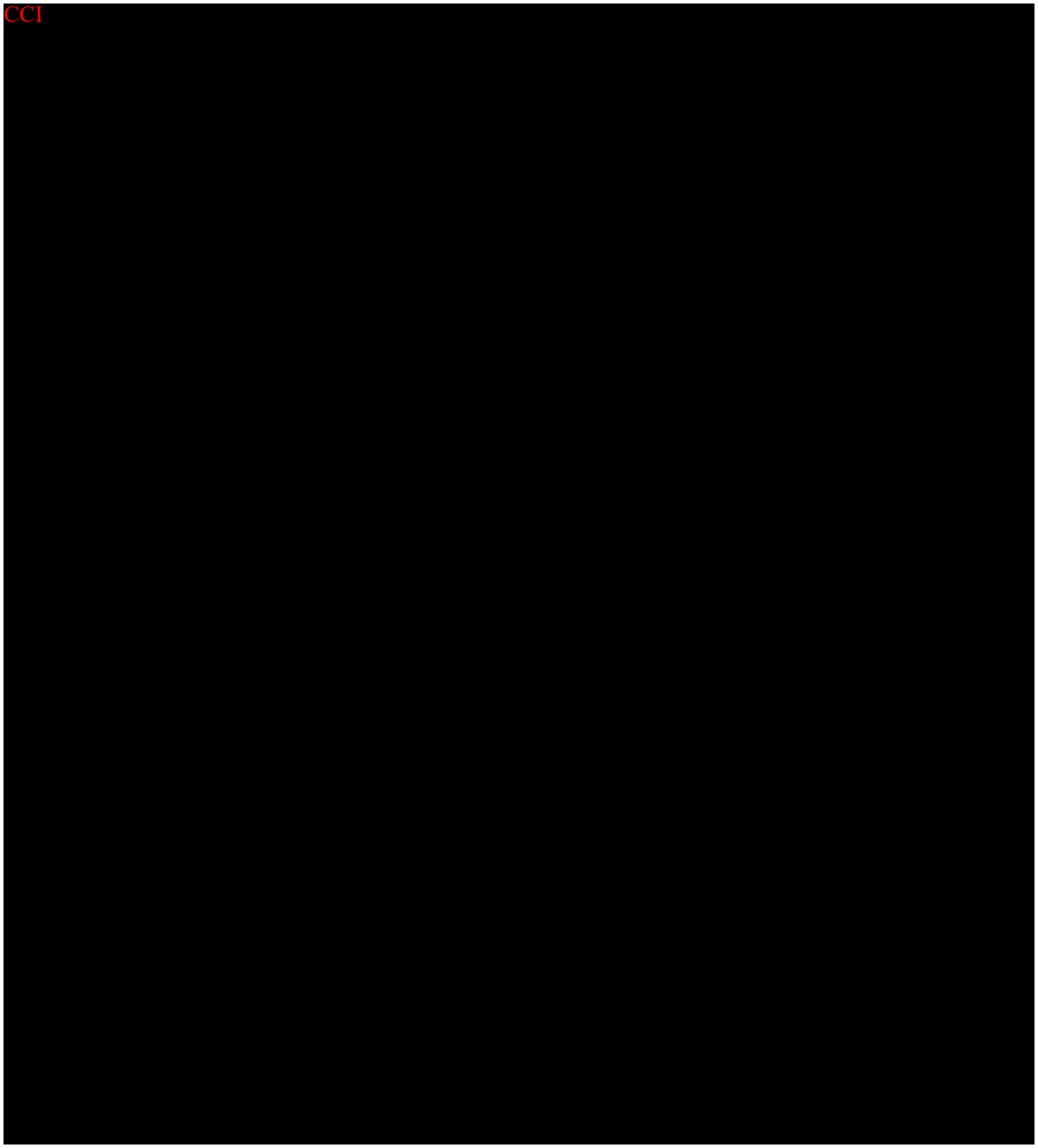
CCI

[redacted]

CCI



CCI



CCI

[redacted]

CCI

[redacted]

CCI

CCI

10.14. Appendix 14: COVID-19

10.14.1. Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

10.14.2. Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrolment and treatment decisions for trial participants.

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

Clinical investigators should document in participant notes as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).

1. Missing protocol-required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

10.14.3. Protocol-Defined Procedures/Visits:

1. Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, and preparation and administration of study intervention (at the discretion of the investigator). It is the responsibility of the investigator or designee to inform GSK when this occurs and to document in the source notes.
2. Remote visits may be performed at the participant's home by qualified study personnel or at a local medical facility, unless the investigator deems that a site visit is necessary.
3. Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the investigator including in the participant's home, if deemed necessary. Biological samples may be collected at a different location, other than the study site (e.g., at participant's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations (see note). Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
4. The PK samples may be collected by a home health nurse to alleviate the burden on participants of frequent visits to the study site
5. If visits to a clinic/home are not feasible, then medical evaluation may take place by telemedicine, which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. GSK will be accountable for working with third party vendors to ensure the site has the required equipment, training and support for this model and should be notified as soon as possible by the investigator that the service is required.
6. As part of this model, study visits may be completed on a virtual platform that connects participants to their investigators and study teams through either a study-issued smartphone or participant's own device (BYOD) model. This technology may be used in combination with visits from mobile study personnel (e.g., mobile nurses) to participants' homes for various lab collections and designated study procedures.
7. The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, imaging or ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary. Participants can also request a timely secure videoconference with the investigator and/or site staff.
8. The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised informed consent form if required.

IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

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

10.14.4. Study Intervention(s)

1. If allowed by country regulation/ethics, then study intervention (including rescue study medication and ancillary supplies related to Investigational Medicinal Product (IMP) administration) can be shipped direct-to-participant (DTP) from the investigational site to the participant's home address. The process for this shipment must be agreed with GSK who will provide the relevant documentation and links to courier sites required to ensure shipments are adequately temperature controlled (if required) throughout transportation

2. Staff at each clinical study centre or the home healthcare professional will be responsible for preparation of study intervention according to procedures detailed in the SRM. No special procedures for the safe handling of study intervention are required.

3. The Principal Investigator assumes GCP responsibilities for IMP handling and the medical control for dispensing to participants. Site Staff should document the dispensing in the Dispensing/Accountability Logs adding a comment that this was a DTP dispensing.

4. Compliance with study intervention administration will be verified through observation by study staff or trained home healthcare professionals.

5. In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

10.14.5. Data Management/Monitoring

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

2. eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilised during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a backup for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
3. Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

10.15. Appendix 15: Abbreviations and Trademarks

AAP	American Academy of Pediatrics
ADA	anti-drug antibody
ADE	adverse device effects
AE	adverse event
ALT	alanine aminotransferase
AUC	area under the curve
BFI	Brief Fatigue Inventory
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRSwNP	chronic rhinosinusitis with nasal polyps
CSR	clinical study report
CV	cardiovascular
EAP	expanded access program
EC	Ethics Committee
ECG	electrocardiogram
eCRF(s)	electronic case report form(s)
EDTA	ethylenediaminetetraacetic acid
EGPA	eosinophilic granulomatosis with polyangiitis
EMA	European Medicines Agency
EUA	emergency use authorisation
FAAN	Food Allergy and Anaphylaxis Network
FEV	forced expiratory volume
FOCP	females of childbearing potential
F/P	FIP1L1-PDGFRα fusion tyrosine kinase gene translocation
FVC	forced vital capacity
GCP	good clinical practice
GSK	GlaxoSmithKline
hCG	human chorionic gonadotrophin
HCP	healthcare provider
HCRU	healthcare resource utilisation
HES	hypereosinophilic syndrome
HIV	human immunodeficiency virus
HBsAg	hepatitis B surface antigen
IDMC	independent data monitoring committee
IB	investigator’s brochure
ICF	informed consent form
ICH	International Conference for Harmonisation

ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IgE	immunoglobulin E
IgG1	immunoglobulin G1
IL-5	interleukin-5
INFα	interferon alpha
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous(ly)
IVRS	IVRS Interactive Voice Response System
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
NAb	neutralising antibodies
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
OCS	oral corticosteroids
OLE	open-label extension
PD	pharmacodynamic
PK	pharmacokinetics
PPPSF-F	Parent Proxy SF v2.0 - Fatigue 10a
PPSF-F	PROMIS Paediatric Short Form v2.0 – Fatigue 10a
PRO	patient-reported outcome
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected using Fridericia's formula
QTL	quality tolerance limits
RNA	ribonucleic acid
SADE	serious adverse device effects
SAE	serious adverse event
SC	subcutaneous(ly)
SE	standard error
SoA	Schedule of Activities
SoC	standard of care
SRM	study reference manual
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
WPAI-HES-CG	Work Productivity and Activity Impairment: HES Caregiver

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
None

10.16. Appendix 16: Protocol Amendment History

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

Amendment 03 (21 August 2023)

This amendment is considered to be substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC and EU Clinical Trial Regulation No. 536/2014 of the European Parliamentof the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This protocol has been amended to add the hepatitis B DNA and hepatitis D antibody test in the liver stopping criteria and to remove the optional Genetics and Biomarker sub-studies. Minor edits made to the footnotes in the schedule of activities for clarification in the eDiary completion. Few sections have been updated in accordance with GSK template and EU CTR (Regulation [EU] No 536/2014). Country specific requirements (Italy) appended to the protocol.

Other administrative changes and minor editorial corrections were also made throughout the document for better clarity.

Section # and title	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities Table 1 Schedule of Activities	Footnote no. 6 and 24 updated to clarify the eDiary completion for patients of 6-11 years of age. Removed details about sample collection for optional genetics and biomarker sub-studies	To reflect the clarification for eDiary entries for patients of 6-11 years and to align with removal of optional genetics and biomarker sub-studies
Section 5.2 Exclusion Criteria Other Exclusions:	Updated the note to add local 12-lead ECG machine read values	To allow use of local 12-lead ECG machine reading to be done prior to visit 2
Section 7.2 Participant Discontinuation/Withdrawal from the Study	Editorial changes made in the text and statement added for withdrawal due to AE/SAE as per GSK template	To add clarity on withdrawal due to AE/SAEs

Section # and title	Description of Change	Brief Rationale
Section 8. Study Assessment and Procedures	Added text regarding collection of demographic data (sex, race and ethnicity) and medical history for monitoring diversity in the trial participants as per GSK template.	To clarify the reason for collection of specific demographic data
Section 8.1.6 PROMIS Paediatric Short Form (SF) v2.0 – Fatigue 10a	Added text "at the time of enrolment" to specify the use of the relevant forms based on participant's age at the time of enrolment	To add clarity that endpoints measurements are based on participant's age at the time of enrolment
Section 8.7 T-cell Profile	Section amended to allow previous or local laboratory T-cell value to be used to rule out lymphoma to determine study eligibility	To allow historical T-cell profiling to be used to assess lymphoma risk
Section 8.9 Genetics	Optional genetics analysis component of the study has been removed and related appendix deleted	To record information provided in the protocol clarification letter dated; 22 November 2022 and memo to the investigators (dated; 06 July 2023) explaining the data generated with the optional genetic sub-studies will not provide any significant valuable information due low number of participants
Section 8.10 Biomarker	Optional biomarker analysis component of the study has been removed	To address the information mentioned in the memo to the investigators (dated; 06 July 2023) explaining the data generated with the optional biomarkers sub-studies will not provide any significant valuable information due low number of participants
Section 9.4.3 Other endpoints	Removed endpoint "Taking immunosuppressive and/or cytotoxic HES therapy at Week 52 in participants that are taking immunosuppressive and/or cytotoxic HES therapy	Removed endpoint is part of aforementioned criteria for treatment failure "Presence of HES flare during the 52-week study treatment period".

Section # and title	Description of Change	Brief Rationale
	at baseline" from considering treatment failure. Statement related to optional biomarkers analysis as part of exploratory efficacy endpoints has been deleted	To align with removal of optional biomarker sub-study
Section 10.1.1 Regulatory and Ethical Consideration	Added applicable EU CTR regulation (EU Regulation [EU] No 536/2014)	Regulatory requirement (EU CTR)
Section 10.1.4 Recruitment Strategy	Newly added sub-section to document the recruitment strategy	Regulatory requirement (EU CTR)
Section 10.1.5 Data Protection	Section updated for describing the measures that will be implemented in case of data security breach as per regulatory requirement (EU CTR)	Regulatory requirement (EU CTR)
Section 10.1.7 Dissemination of Clinical Study data	Section updated to add clarity on the posting of the clinical study data for EU CTR compliance	Regulatory requirement (EU CTR)
Section 10.1.10 Study and Site start and Closure	Minor edits in the definition of the study start date. Reason added for study termination	Clarification of intent
Section 10.2 Appendix 2, Table 8 Protocol-Required Safety Laboratory Tests	Added wording on the use of central laboratories for parasitic screening with stool microscopy. Wording added to specify that the central laboratory will only detect the pre-listed organisms and alternative testing, or specialist reviews can be arranged if required	To allow use of central laboratories for stool microscopy test for parasitic screening and clarification added if alternative tests or specialist reviews are required in certain cases
Previous Section 10.5 Appendix 5: Genetics	Section deleted	Section deleted due to removal of optional genetics analysis sub-study
Section 10.5 Appendix 5: Liver Safety,	Footnote 4. Updated for addition of test for Hepatitis B	To address the protocol clarification letter dated

Section # and title	Description of Change	Brief Rationale
(Table 9: Liver chemistry stopping criteria)	DNA and Hepatitis D antibody in certain circumstances	12 October 2022, which clarifies the Hep B DNA and Hep D tests
Section 10.15 Appendix 15 Country Specific requirement	Newly added appendix as per GSK template Added country specific requirements for Italy (exclusion criteria)	Country specific regulatory requirements integrated in the global protocol amendment as per GSK template and regulatory requirement (EU CTR)
Throughout the document	Re-numbering of the subsections and the appendices. Updated cross referencing to relevant sections/appendices	Due to addition and/or deletion of sections and subsections

Amendment 02 ITA 1:09 June 2022

Overall Rationale for the Amendment

This protocol has been amended principally to add the option of performing the V1 (screening) blood eosinophil test at a local lab to enable faster testing of the sample than might be possible when sending it to the central lab.

Section # and Name	Description of Change	Brief Rationale
Title Page	Addition of Study Phase (3) to the protocol title	Regulatory commitment to the Argentinian Regulatory Authority
1.3 Schedule of Activities (SoA)	Inclusion of footnote 14 allowing eosinophil count test to be performed locally	To minimize the amount of time between the sample being taken and the sample being tested.
2.1 Study Rationale	Updated the approved countries of mepolizumab and the indication statement.	To reflect the latest approval status of mepolizumab and slight variations in the indication statement by country.
8. Study Assessments and Procedures	Addition of option to test eosinophil samples at screening at local labs.	To minimize the amount of time between the sample being taken and the sample being tested.
8.9 Genetics	Addition of blood volume drawn for the optional Genetic sample	Regulatory commitment to the Spanish Regulatory Authority
10.2. Appendix 2: Clinical Laboratory Tests	Addition of option to test eosinophil samples at screening at local labs.	To minimize the amount of time between the sample being taken and the sample being tested.

Amendment 2: 09 June 2022

Overall Rationale for the Amendment

This protocol has been amended to add the option of performing the V1 (screening) blood eosinophil test at a local lab to enable faster testing of the sample than might be possible when sending it to the central lab. Footnote 22 of the Schedule of Events table also has the added clarification that it is recommended the optional genetic sample to be taken at visit 3 for participants 30Kg or under to reduce blood draw burden at the visit.

Section # and Name	Description of Change	Brief Rationale
Title Page	Addition of Study Phase (3) to the protocol title	Regulatory commitment to the Argentinian Regulatory Authority
1.3 Schedule of Activities (SoA)	Inclusion of footnote 14 allowing eosinophil count test to be performed locally Footnote 23 modified to add. Genetic sample collection is recommended at Visit 2 for participants over 30Kg and at Visit 3 for participants 30Kg or under, but may be drawn at any time after the participant is consented and enroled.	To minimize the amount of time between the sample being taken and the sample being tested. To reduce the blood draw volume demand for participants 30kg or under at Visit 2.
2.1 Study Rationale	Updated the approved countries of mepolizumab and the indication statement.	To reflect the latest approval status of mepolizumab and slight variations in the indication statement by country.
8. Study Assessments and Procedures	Addition of option to test eosinophil samples at screening at local labs.	To minimize the amount of time between the sample being taken and the sample being tested.
8.9 Genetics	Addition of blood volume drawn for the optional Genetic sample	Regulatory commitment to the Spanish Regulatory Authority
10.2. Appendix 2: Clinical Laboratory Tests	Addition of option to test eosinophil samples at screening at local labs.	To minimize the amount of time between the sample being taken and the sample being tested.

Amendment 01 ITA 1:22 March 2022

Overall Rationale for the Amendment

This protocol has been amended principally to add a minimum weight and estimated Glomerular Filtration Rate (eGFR) threshold based on available data as well as exclusion of subjects affected by hereditary fructose intolerance to the study population criteria. Footnote 22 of the Schedule of Events table has the added clarification that it is recommended the optional genetic sample to be taken at visit 3 for participants 30Kg or under to reduce blood draw burden at the visit.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Footnote 22 modified to add. Genetic sample collection is recommended at Visit 2 for participants over 30Kg and at Visit 3 for participants 30Kg or under, but may be drawn at any time after the participant is consented and enroled.	To reduce the blood draw volume demand for participants 30kg or under at Visit 2.
5.2 Exclusion Criteria	1. Addition to Exclusion Criteria 16 to exclude participants with hypersensitivity to mepolizumab drug components including participants with hereditary fructose intolerance 2. Addition of Exclusion Criteria 20 specifying a minimum bodyweight of 15Kg 3. Addition of Exclusion Criteria 21 specifying a minimum eGFR threshold 50mL/min	1. Clarification of which hypersensitivities should be excluded from the study. 2. GSK mepolizumab drug exposure simulations have data for 15Kg and above. 3. Data for the dose of mepolizumab not requiring modification extends to 50mL/min eGFR.

Amendment 1: 02 August 2021

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	1. Complete eCRF added at V1 2. Clarified discontinuation visits replace visits 2-15 3. Footnote 3 added subjects who prematurely discontinue study treatment will continue to attend 4-weekly scheduled 4. Footnote 6 following text added 'weekly, when translations become available' 5. Footnote 11 is reworded 'Only SAEs that are considered related to study procedures are to be collected from the time of signing informed consent.' 6. Footnote 14 added clinical chemistry and urinalysis follow test frequency of Treatment Period schedule visit 2-15 for treatment discontinued participants 7. Footnote 16 added to clarify pregnancy testing is required until 12 weeks after the last dose 8. Footnote 20 added Immunogenicity is to be performed 4 and 12 weeks after the last dose only 9. Footnote 21 added PK is to be performed 4 weeks after last dose only	1. Corrections and clarifications of the schedule of activities

Section # and Name	Description of Change	Brief Rationale
	10. Footnote 25 the following text in added 'when translations become available' 11. Footnote 26 added 'Review AEs and participant questionnaires, identify HES flares and check questionnaire compliance' 12. Immunogenicity tests added to the early treatment discontinuation and withdrawal visits. 13. PK sample added at the discontinuation and withdrawal visits 14. Visit 3 and Visit 4 are now site visits only 15. Added collection of PROs at withdrawal visits 16. Removed collection of eDiary at the withdrawal visits	
5.5. Screen Failures	The following text is added 'including ethnicity and race where permitted by local regulations'	To clarify which demographic data will be gathered
6.1. Study Intervention(s) and Concomitant Therapy	Anaphylaxis text added from section 6.4.	Text was more suitable in this section as it didn't relate to compliance
6.2. Preparation/ Handling/ Storage/Accountability of Study Intervention	Study intervention storage condition sentence is restructured	To clarify refrigerated storage conditions for the study intervention
6.4. Study Intervention Compliance	1. Epinephrine rescue medications added as a requirement for sites and home nurses to have available	1. To specify the medication for acute severe reaction 2. Better fit for text in 6.1.

Section # and Name	Description of Change	Brief Rationale
	during all mepolizumab administration 2. Text moved to section 6.1.	
7.1. Discontinuation of Study Intervention	Removed consent withdrawal as an example of treatment discontinuation	Consent withdrawal leads to withdrawal from the study.
7.2. Participant Discontinuation/ Withdrawal from the Study	1. Updated section to clarify process for study withdrawal 2. Added reasons for withdrawal from study must be captured in the CRF	1. If a participant withdraws consent a withdrawal visit should be performed if possible 2. Highlighting of important eCRF requirement
8.1.2. HES Core Assessments v2 (Clinician Assessment)	The process of capturing the data is updated to 'in the eCRF'	Correction that the HES Core assessment is captured in the study eCRF
8.1.6. PROMIS Paediatric Short Form (SF) v2.0 – Fatigue 10a	The following text is added 'when translations become available'	To allow flexibility to not perform the PPSF and PPPSF questionnaires in countries where translations are not available
8.3.8- Medical Device Deficiencies	1. Added as study intervention to 'Medical devices are being provided for use in this study'	1. Added for clarification
8.3.8.1. Time Period for Detecting Medical Device Deficiencies	Bullet added for 'associated persons'	Collection of AE/SAEs in spouses, care givers, site staff, etc. that handle the medical devices is now required. Wording added throughout this section.
8.3.8.2 Follow-up of Medical Device Deficiencies	Wording added for associated persons'	Collection of AE/SAEs in spouses, care givers, site staff, etc. that handle the medical devices is now required. Wording added throughout this section.

Section # and Name	Description of Change	Brief Rationale
8.3.8.3. Prompt Reporting of Medical Device Deficiencies to the Sponsor	The Medical Device Deficiency Report Form collection process updated	Paper forms to be used and email to be sent to GSK
8.7. T-Cell Profile	T-cell profile updated	T-cell profile was revised since protocol V1.
8.9. Genetics	1. and/or Pharmacogenomics' removed 2. Reference to Biomarker Plan removed	1. Removed to align with Appendix 5 (Section 10.5) 2. Document does not contain study level information on genetic testing
8.10. Biomarker	1. Text added that biomarkers are to be taken after written consent 2. Description of potential biomarker tests removed	1. To clarify optional consent requirement for this assessment 2. Further analysis and storage of biomarker samples will not be performed. Samples are destroyed after analysis.
9.4.2 Secondary Efficacy Endpoints	Changes to intercurrent event wording	To clarify estimands for secondary endpoints
9.4.3- Other Endpoints	1. Added /or cytotoxic to other endpoint text 2. Changes to intercurrent event wording	1. For consistency in the protocol 2. To clarify estimands for other endpoints
10.1.3 Informed Consent and Assent Process	1. Added text to 1st bullet point ('including the risk and benefits') 2. Added consent process for medical device incidents incurred by 'associated persons'	1. Discussion of risks and benefits is part of the informed consent process. Consistent with Article 29, #2 ("Informed Consent") of EU regulation No. 536/2014 2. The associated person consent is a new requirement
10.1.9. Study and Site Start and Closure	The text 'and' is removed	The sentence is restructured for clarity

Section # and Name	Description of Change	Brief Rationale
10.2 Clinical Laboratory tests	Additional footnote added	Clarification of testing expected for routine urinalysis and pregnancy testing
10.3.2. Definition of SAE	Definition corrected	Definition was unclear
10.3.4. Recording and Follow-Up of AE and SAE	Assessment of Intensity updated	Definitions updated to align with CDISC
10.3.5. Reporting of SAE to GSK	72 hour check box requirement removed	This requirement is no longer in effect. The need for PIs to document in the medical notes that they have reviewed the AE/SAE and provide an assessment of causality is still covered by wording in Section 10.7.4.
10.7.1 Definition of Medical Device AE	SAE definition text added: events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.	For further clarification
10.7.3, Device Deficiency		Device deficiency also includes inadequacy of the information supplied by the manufacturer
10.7.4Recording and Follow-Up of AE and/or SAE and Device Deficiencies	Assessment of Intensity updated	Definitions updated to align with CDISC
10.7.6. Reporting of SADEs	1. The following statement is added 'Refer to the paper medical device deficiency report form for details on transmission of this information to the sponsor.' 2. Reference to SAE contacts in SRM removed	1. Update on the location of contact information for the submission of the paper medical device deficiency report form

Section # and Name	Description of Change	Brief Rationale
10.7.7. Reporting of Medical Device Deficiencies for Associated Person	New section added	Provides guidance for the Device Deficiencies for Associated Person requirement.
10.9 HES Core Assessment v2 (Clinician Assessment)	Additional footnotes for cardiovascular classification added	Classification and references provided for heart failure classification

11. REFERENCES

Aljebab F, Choonara I, Conroy S. Systematic Review of the toxicity of long-course oral corticosteroids in children. *PLoS ONE.* 2017;12(1):e0170259. doi:10.1371/journal.pone.0170259

American Heart Association. Classes of Heart Failure. Available at: https://professional.heart.org/en/guidelines-and-statements/classification. Accessed 05 July 2021.

Burris D, Rosenberg CE, Schwartz JT, Zhang, Eby MD, Abonia JP, et al. Pediatric hypereosinophilia: characteristics, clinical manifestations, and diagnoses. *J Allergy Clin Immunol Pract.* 2019;7(8):2750-2758.e2. doi:10.1016/j.jaip.2019.05.011

Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med*. 2003;348(13):1201-14. doi: 10.1056/NEJMoa025217

CCI

[redacted]

Han J, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, et al. A Phase 3, randomised, double-blind, placebo-controlled trial of mepolizumab for chronic rhinosinusitis with nasal polyps: the SYNAPSE study. Manuscript submitted 2020.

Hsu DT, Pearson GD. Heart failure in children: part I: history, etiology, and pathophysiology. Circ Heart Fail. 2009 Jan;2(1):63-70.

Klion A. Hypereosinophilic syndrome: current approach to diagnosis and treatment. *Annu Rev Med*. 2009;60:293–306. doi: 10.1146/annurev.med.60.062107.090340

Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol.* 2009;124(6):1319-25.e3. doi:10.1016/j.jaci.2009.09.022

Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. [published correction appears in N Engl J Med. 2015 Apr 30;372(18):1777]. *N Engl J Med.* 2014;371(13):1198-1207. doi:10.1056/NEJMoa1403290

Pavord ID, Korn S, Howarth P, Bleeker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012;380(9842):651-659. doi:10.1016/S0140-6736(12)60988-X

Poetker DM, Reh DD. A comprehensive review of the adverse effects of systemic corticosteroids. *Otolaryngol Clin N Am.* 2010;43(4):753-768. doi:10.1016/j.otc.2010.04.003

PROMIS Fatigue Scoring Manual. Available at: http://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Fatigue_Scoring_Manual.pdf. Accessed 11 March 2021.

Reilly Associates 2002. Health Outcomes Research. http://prosites-margaret.homestead.com/WPAI_Translations-5.html. Accessed 11 March 2021.

Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. *Blood.* 2017;129(6):704-714. doi: 10.1182/blood-2016-10-695973

Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon HU, et al. Treatment of patients with hypereosinophilic syndrome with mepolizumab [published correction appears in N Engl J Med. 2008 Jun 5;358(23): 2530]. *N Engl J Med*. 2008;358(12):1215-1228. doi:10.1056/NEJMoa070812

Roufosse FE, Goldman M, Cogan E. Hypereosinophilic syndromes. *Orphanet J Rare Dis.* 2007;2:37. Published 2007 Sep 11. doi:10.1186/1750-1172-2-37

Roufosse FE, Kahn JE, Gleich GJ, Schwartz LB, Singh AD, Rosenwasser LJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol.* 2013;131(2):461-7 .e75. doi:10.1016/j.jaci.2012.07.055

Roufosse F, Kahn JE, Rothenberg ME, Wardlaw AJ, Klion AD, Kirby SY, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 2020;146(6):1397-1405. doi:10.1016/j.jaci.2020.08.037

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson Jr FN, Bock AS, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006;117(2):391-397. doi:10.1016/j.jaci.2005.12.1303

U.S. Food and Drug Administration (FDA). Collection of Race and Ethnicity Data in Clinical Trials. Guidance for Industry and Food and Drug Administration Staff. FDA Web site. https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf. Issued 26 October 2016. Accessed 05 April 2019.

Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol.* 2012;130(3):607-612.e9. doi:10.1016/j.jaci.2012.02.019

Wechsler ME, Akuthota P, Khoury JP, Klion A, Langford CA, Merkel PA, et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med.* 2017;376(20):1921-1932. doi:10.1056/NEJMoa1702079

Williams KW, Ware JA, Abiodun A, Holland-Thomas NC, Khoury P, Klion AD. Hypereosinophilia in Children and Adults: A Retrospective Comparison. *J Allergy Clin Immunol Pract.* 2016;4(5):941- 941-947.e1. doi:10.1016/j.jaip.2016.03.020

Signature Page for 215360 TMF-20082402 v1.0

Reason for signing: Approved	Name PPD Role: Approver Date of signature: 16-Dec-2024 11:34:24 GMT+0000

Signature Page for TMF-20082402 v1.0