Protocol

Study ID: 218065

Official Title of Study: A post-authorisation safety study (PASS) to describe real-world safety and effectiveness of NUCALA (mepolizumab) in paediatric eosinophilic granulomatosis with polyangiitis (EGPA) patients in Europe.

Date of Document: 23 Sep 2022

TITLE PAGE

Division: Pharma Research and Development
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Title:	A post-authorisation safety study (PASS) to describe real-world safety and effectiveness of NUCALA (mepolizumab) in paediatric eosinophilic granulomatosis with polyangiitis (EGPA) patients in Europe.

Compound Number:	SB-240563
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Effective Date:	23 Sep 2022
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Author(s):	PPD , PPD ; PPD , PPD ; PPD , PPD ; PPD , PPD , PPD , PPD ; PPD , PPD ; GlaxoSmithKline (GSK) PPD , PPD ; Syneos Health
Indication Studied:	Eosinophilic granulomatosis with polyangiitis (EGPA) in paediatric patients aged 6 years and above

PASS INFORMATION

Title	A post-authorisation safety study (PASS) to describe real-world safety and effectiveness of NUCALA (mepolizumab) in paediatric eosinophilic granulomatosis with polyangiitis (EGPA) patients in Europe.
Protocol version identifier	1.0
Date of last version of protocol	26 AUG 2022
EU PAS (ENCEPP) register number	Study not registered yet
Active substance	Mepolizumab - R03DX09
Medicinal product	NUCALA solution in pre-filled pen or syringe, or lyophilised powder for solution
Product reference	EU/1/15/1043/001 to EU/1/15/1043/0010
Procedure number	EMEA/H/C/003860
Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Limited
Joint PASS	No
Research question and objectives	The purpose of this study is to describe real-world safety and effectiveness of mepolizumab in paediatric EGPA patients in Europe.
Country(-ies) of study	Patients will be included from sites in selected countries across Europe.
Authors	PPD, PhD PPD, Respiratory Epidemiology GlaxoSmithKline Inc. 100 Milverton Drive Suite 800 Mississauga, ON, L5R 4H1, Canada PPD, PhD PPD, Epidemiology Syneos Health De Entrée 99-197, 14th floor 1101 HE Amsterdam, The Netherlands

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Limited 12 Riverwalk Citywest Business Campus Dublin 24 Dublin Ireland
MAH contact person	PPD Regulatory Manager Respiratory TG Global Regulatory Affairs GlaxoSmithKline 980 Great West Road, Brentford, Middlesex TW8 9GS United Kingdom

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1. LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADR	Adverse drug reactions
AE	Adverse event
ANCA	Anti-neutrophil cytoplasmic antibodies
CHCC	Chapel Hill Consensus Conference
eCRF	electronic case report form
DoT	Duration of treatment
EDC	Electronic case report form
EGPA	Eosinophilic granulomatosis with polyangiitis
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EP	Enrolled population
EU	European Union
EULAR	European League Against Rheumatism
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GSK	GlaxoSmithKline
GVP	Good Pharmaco Vigilance Practice
HCP	Healthcare provider
ICF	Informed consent form
ICH	International Conference on Harmonisation
IL-5	Interleukin-5
IRB	Institutional review board
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
OCS	Oral corticosteroid (prednisone/prednisolone)
PASS	Post-authorisation safety study
PEF	Peak expiratory flow
PT	Preferred term
PVAS	Paediatric Vasculitis Activity Score
PVDI	Paediatric Vasculitis Damage Index
SAE	Serious adverse event
SMA	Site management associate
SMP	Safety management plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Safety population
VEO	Value, Evidence and Outcomes
WHO	World Health Organization

Trademark Information

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NUCALA

Trademarks not owned by the GlaxoSmithKline group of companies
SAS

2. RESPONSIBLE PARTIES

Scientific Lead	PPD, PhD PPD, Respiratory Epidemiology GlaxoSmithKline Inc. PPD

Contact details of all Investigators participating in the study will be kept in a stand-alone document listed in ANNEX 1.

SPONSOR INFORMATION PAGE

Study ID: 218065

Sponsor Legal Registered Address:

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

Sponsor Serious Adverse Events (SAE) Contact Information:

UK.GSK-RD-GCSP-CTSM-ADMIN@GSK.COM

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

3. ABSTRACT

3.1. Title

A post-authorisation safety study (PASS) to describe real-world safety and effectiveness of NUCALA (mepolizumab) in paediatric eosinophilic granulomatosis with polyangiitis (EGPA) patients in Europe.

Version 1.0, 26 August 2022, PPD , GlaxoSmithKline & PPD , Syneos Health

3.2. Rationale and Background

EGPA is a rare autoimmune disease and is characterised by small vessel vasculitis in association with asthma, sinusitis, and pulmonary infiltrates. Multiple organs can be affected including the heart, lungs, skin, gastrointestinal tract, kidneys, and nervous system [Keogh, 2006; Vaglio, 2012; Holle, 2009].

Paediatric EGPA is extremely rare, with approximately 100 cases identified in the literature through 2020 [GSK, data on file]. In a GSK analysis, paediatric data from published literature were supplemented with individual case reports, and these pooled results were analysed by system organ class [GSK, data on file]. This population was indirectly compared with a pooled population of adult-onset EGPA patients, also from published literature [Sablé-Fourtassou, 2005; Sinico, 2005]. The analysis showed that both childhood-onset and adult-onset EGPA are characterised by marked blood eosinophilia, asthma and sinusitis, and that many clinical features of childhood-onset and adult-onset EGPA are generally similar.

Eosinophilia is central to the pathogenesis of EGPA, and human interleukin 5 (IL-5) is a key cytokine regulating the life cycle of the eosinophil. Neutralization of IL-5 with mepolizumab therefore offers a potential therapeutic option for EGPA. Mepolizumab a humanised monoclonal antibody (IgG1, kappa, mAb), binds with high specificity and affinity to IL-5, the key cytokine responsible for regulation of blood and tissue eosinophils. The clinical program to support the indication for use of mepolizumab in patients with EGPA consists primarily of a single, Phase III study in adults. The study comprised a 52-week study treatment period and an 8-week follow-up period [Wechsler, 2017]. Due to the very low incidence and prevalence of EGPA in the paediatric population, a clinical trial was not considered feasible to support the paediatric indication. In this context, only individual case reports about the use of mepolizumab have been reported in paediatric patients aged 6 to 17 years [Joseph, 2018; Nara, 2019; Awouters, 2021].

To address a request from the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) to generate data for mepolizumab in the post-marketing setting in paediatric patients aged 6 to 17 years in Europe, this post-authorisation safety study (PASS) aims to collect information on real-world safety and effectiveness in paediatric EGPA patients treated with mepolizumab from sites across Europe in a case-series.

3.3. Research Question and Objective(s)

The purpose of this PASS is to describe the real-world safety and effectiveness in individual paediatric EGPA patients (i.e., a case-series) treated with mepolizumab in Europe. Given the ultra-rare nature of the disease, a comparison group of EGPA patients who are not treated with mepolizumab will not be included in this study. This study will focus on the occurrence of adverse events and change in oral corticosteroid (OCS) dosage after initiating mepolizumab.

Objectives	**Description**
Primary Objective	To describe the real-world safety of mepolizumab treatment in paediatric EGPA patients aged 6 to 17 years
Secondary Objectives	• To describe the real-world effectiveness of mepolizumab treatment in terms of the effect of mepolizumab on OCS dosage • To describe paediatric EGPA patients treated with mepolizumab per routine clinical care in terms of demographics, clinical characteristics, medical and treatment history

3.4. Study Design

This multinational, multi-site, case-series will aim to collect data on real-world safety and effectiveness of up to 24 months after the initiation of mepolizumab treatment in paediatric EGPA patients in Europe. In addition, demographic and relevant medical history data will be collected up to 12 months prior to the first dose of mepolizumab.

All eligible paediatric EGPA patients aged 6-17 years who initiated mepolizumab in the 12 months prior to the enrolment start date (regardless of whether they continue treatment following study enrolment or not), or who will initiate mepolizumab treatment at or after the enrolment start date will be invited for study enrolment by their treating physicians. These physicians will be from specialised centres and hospitals known to treat paediatric EGPA patients from selected countries in Europe.

As the study is non-interventional, the decision to treat paediatric EGPA patients with mepolizumab will be made prior to and independent from the decision to enrol patients into the study, and baseline and follow-up assessments will be in accordance with local standard medical care.

After obtaining informed consent from parents/caregivers and assent from paediatric patients, they will be enrolled into the study and data will be extracted from medical records and entered in an electronic case report form (eCRF).

Depending on the time point of the initiation of mepolizumab treatment in relation to the enrolment start date (i.e., the study start date), data for the primary and secondary objectives will be collected either prospectively (primary analysis) and/or retrospectively (supplemental analysis).

At enrolment, data from medical records before the initiation of mepolizumab treatment will be collected. These data will include available demographic and relevant medical history up to 12 months prior to the first dose of mepolizumab. Mepolizumab treatment

information (e.g., dose and duration), safety data (adverse events [AEs], serious AEs [SAEs], pregnancy exposures and medical device incidents), and effectiveness data (i.e., the effect of mepolizumab on OCS dosage) will be extracted from medical records from the first dose of mepolizumab until the end of follow-up. Patients will be followed for a maximum of 24 months after the first dose of mepolizumab, or until study discontinuation for any reason, or up to 12 months after mepolizumab treatment discontinuation; whichever comes first.

Subjects that permanently stop mepolizumab are not required to withdraw from the study. If for any reason a subject permanently stops mepolizumab, every effort should be made by the Investigator to keep the subject in the study to collect important safety and effectiveness data up to 12 months after mepolizumab treatment discontinuation.

The Investigator or their designee will collect AE, SAE and medical device incident information until the AE, SAE or medical device incident is resolved or stabilised, or until the last study visit within routine care; whichever comes first. Pregnancies will be followed up to determine outcome (including premature termination). In addition, after the last study visit within routine care of each patient, physicians will provide a narrative/opinion on the benefit/risk profile of mepolizumab.

The Investigator or their designee will extract data from medical records at routine care (scheduled and unscheduled) visits as they occur. Patients who are not seen for a period of 6 months will be contacted directly by the Investigator or their designee to collect minimal patient safety information, provided that this contact is considered by their physician to be within the standard of care for this patient.

The total study duration is estimated to be a maximum of 7 years based on a planned study enrolment period of 5 years and a follow-up period of 24 months after the first dose of mepolizumab. Annual interim reviews of study progress and patient numbers are planned to monitor feasibility.

3.5. Study Population

The study will include paediatric EGPA patients treated with mepolizumab as part of routine clinical care from sites in selected countries in Europe.

Inclusion Criteria:

A patient who meets **all** of the following criteria is eligible for inclusion:

- Written informed assent and parent/caregiver consent
- Male or female, aged 6 to 17 years at the start of mepolizumab treatment
- Confirmed diagnosis of EGPA
- Initiated mepolizumab up to 12 months prior to enrolment start date (regardless of whether they continue treatment following study enrolment or not) or scheduled to receive treatment with mepolizumab at or after enrolment per routine clinical care.

Exclusion Criteria:

A patient who meets **any** of the following criteria is not eligible for inclusion:

- Concurrent enrolment and/or participation in an interventional clinical trial involving either an investigational medicinal product or medical device
- Received treatment with mepolizumab more than 12 months prior to enrolment start date
- Received other biologics within 3 months of the first dose of mepolizumab.

3.6. Variables

- Demographics (e.g., age at diagnosis, age at mepolizumab initiation and age at enrolment, sex)
- Clinical characteristics (e.g., EGPA disease status and features, absolute eosinophil level, anti-neutrophilic cytoplasmic antibody [ANCA]-positive status) using the most recent data available up to 12 months before the index date, i.e., the first dose of mepolizumab, or at diagnosis
- Comorbidities at the index date (most recent data available up to 12 months before the index date or at diagnosis) and during follow-up
- Treatment history (EGPA management and concomitant medications up to 12 months before the index date)
- Mepolizumab treatment details including dose, duration and (reasons for) discontinuation, dose delays/interruptions and dose changes at the index date and during follow-up
- OCS and immunosuppressant use including type, dose, duration and (reasons for) discontinuation and dose changes as well as details other prescribed treatments at the index date and during follow-up
- Safety data: AEs, SAEs, pregnancy exposures and medical device incidents at the index date and during follow-up
- Physicians will provide a narrative/opinion on the benefit/risk profile of mepolizumab.
- Additional variables to extract, if data is available:
    - EGPA American College of Rheumatology (ACR)/Lanham criteria at diagnosis
    - Respiratory and cardiac involvement during follow-up
    - Absolute eosinophil counts (% change of baseline) during follow-up
    - EGPA disease status (remission, relapse or refractory) during follow-up
    - Asthma exacerbations prior to the index date and during follow-up
    - Paediatric Vasculitis Activity Score [PVAS] and Paediatric Vasculitis Damage Index [PVDI] score at the index date and during follow-up
    - Spirometry measurements at the index date and during follow-up
    - Hospital admissions at the index date and during follow-up

3.7. Data Sources

Clinical data of paediatric EGPA patients enrolled into this study from sites in selected countries across Europe will be extracted by Investigators or their designees into the eCRF. The most populous countries within Europe will be selected. Sites within countries will be selected based on their EGPA expertise and catchment area. All data elements

will be extracted from information routinely recorded in medical records by the Investigator or their designee for the purposes of the study. Where required, patient/guardian self-report, hospital discharge summaries or other relevant healthcare records will be requested by the investigator or site staff for all SAEs among enrolled patients. In addition, physicians will provide a narrative/opinion on the benefit/risk profile of mepolizumab.

3.8. Study Size

Based on existing patient registries, healthcare databases and published case-series, at most 13 paediatric EGPA patients are expected to be diagnosed over a five-year period across the selected European countries of whom about 10 patients might be prescribed mepolizumab and willing to participate. The feasibility of the study will be evaluated on an annual basis.

3.9. Data Analysis

Data from this study will be described per patient as a case series, as the sample size will be insufficient to perform statistical analyses or summarise across patients. Given the ultra-rare nature of the disease, a comparison group of EGPA patients who are not treated with mepolizumab will not be included in this study and no formal hypotheses will be tested.

Analysis Populations:

Two analysis populations will be defined:

- Enrolled Population (EP) - All patients for whom written informed assent and parent/caregiver consent has been obtained. The EP will be used to assess reasons for not initiating mepolizumab while being scheduled to initiate mepolizumab after enrolment
- Safety Population (SP) - All patients in the EP who received at least one dose of mepolizumab. The SP will be used for descriptive, safety and effectiveness analyses

Statistical Methods:

The primary analysis will present case reports of patients who initiated mepolizumab treatment at or after the enrolment start date. The primary analysis will be supplemented with patients that had started mepolizumab prior to the enrolment start date.

For the primary and secondary objectives, the variables in Section 3.6 will be described **per patient** in the SP according to whether follow-up data was extracted before (retrospective) or after (prospective) the enrolment start date.

Missing data will not be imputed.

3.10. Milestones

This study is projected to begin enrolment in Q4 2022. Data collection will end in Q3 2029. The final study report is planned to be completed in Q4 2029.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Enrolment start date: Data collection will start at the time of study enrolment of the first patient into the study from Q4 2022.

Index date: Data will be extracted from medical records by the Investigator or their designee and entered in the eCRF throughout a maximum of 24 months follow-up from the first dose of mepolizumab which is defined as index date.

Study progress: Reports will be developed annually; expected timelines are provided in the table below.

Study end: Data collection will continue until the end of the study (7 years), until target enrolment is achieved of approximately 10 evaluable paediatric EGPA patients, or until early study closure (due to low recruitment rates or insufficient data availability).

Milestone	**Planned date**
Start of data collection	Q4 2022
End of data collection	Q3 2029
Study progress report 1	Q4 2023
Study progress report 2	Q4 2024
Study progress report 3	Q4 2025
Study progress report 4	Q4 2026
Study progress report 5	Q4 2027
Study progress report 6	Q4 2028
Registration in the EU PAS register	Q4 2022
Final report of study results	By Q4 2029

6. RATIONALE AND BACKGROUND

6.1. Background

6.1.1. Nature of EGPA Disease

EGPA is a rare autoimmune disease and is characterised by small vessel vasculitis in association with asthma, sinusitis, and pulmonary infiltrates. Multiple organs can be affected including the heart, lungs, skin, gastrointestinal tract, kidneys, and nervous system [Keogh, 2006; Vaglio, 2012; Holle, 2009].

Paediatric EGPA is extremely rare, with approximately 100 cases identified in the literature through 2020 [GSK, data on file]. In a GSK analysis, paediatric data from published literature were supplemented with individual case reports, and these pooled results were analysed by system organ class [GSK, data on file]. This population was indirectly compared with a pooled population of adult-onset EGPA patients, also from published literature [Sablé-Fourtassou, 2005; Sinico, 2005]. The analysis showed that both childhood-onset and adult-onset EGPA are characterised by marked blood eosinophilia, asthma and sinusitis, and that many clinical features of childhood-onset and adult-onset EGPA are generally similar.

Unfortunately, as compared with adult-onset EGPA, paediatric EGPA has a higher mortality rate with increased pulmonary and cardiac involvement and heightened concerns regarding traditional cytotoxic therapy, OCS use, and long-term immunosuppression [Zwerina, 2009]. Regarding the latter, immunosuppressive and steroid-related side effects include are not limited to Cushing's syndrome, osteoporosis, growth delay and infections, regularly occurred. Regarding disease severity, the rate of relapse has been described to be significantly higher in paediatric patients (64.3%) than in adult patients (25.3%). Taken together, therefore more specific therapeutic options for EGPA are required to reduce therapy-related adverse events, especially in paediatric patients [Nara, 2019].

6.1.2. Current Therapies and Unmet Medical Need

The approach to the management of EGPA is based on reduction of active inflammation, suppression of the immune response, and treatment of disease-specific and/or treatment-related complications. Corticosteroid therapy is the cornerstone therapy for the treatment of both poor- and good-prognosis EGPA patients. However, use of corticosteroids, particularly longer-term, is associated with significant side effects, including weight gain, osteoporosis, hyperglycaemia, depression, and increased risk of infection, which can limit the benefits [Poetker, 2010; Sarnes, 2011; Strehl, 2016]. Furthermore, although remission can be achieved in a proportion of patients with corticosteroid therapy alone, addition of more potent immunosuppressive therapies (e.g., azathioprine, methotrexate, or mycophenolate mofetil) to maintain remission is commonly required [Baldini, 2010; Vaglio, 2012; Dunogué, 2011; Holle, 2009; Mukhtyar, 2009]. Depending on disease activity, i.e., active severe EGPA or active non-severe EGPA, different treatment combinations are suggested in order to achieve clinical remission [Chung, 2021]. Although the use of these treatments is effective for establishing remission, patients

remain vulnerable to either the complications of the long-term use of these therapies, or to the risk of relapse, particularly if the dose of corticosteroid is reduced. Relapses are common and have been found to increase in frequency with time [Baldini, 2010; Ribi, 2008; Dunogué, 2011; Comarmond, 2013; Samson, 2013; Mahr, 2014; Yates, 2016]. Furthermore, recurrent relapse is considered to place the patient at risk of permanent tissue and/or organ damage secondary to the vasculitic process. Therefore, there is an unmet need in the treatment of EGPA to induce and maintain remission and to prevent relapse while reducing the burden of corticosteroid usage and other immunosuppressive therapies.

In paediatric patients aged 6 to 17 years, the therapies used to manage EGPA are similar to those used in adults, i.e., systemic corticosteroids with adjunct use of immunosuppressive and/or cytotoxic agents where necessary [Boyer, 2006]. Treatment aims to improve symptoms and to suppress/reduce eosinophil count to prevent peripheral tissue/ neurological infiltration and damage by inflammation which leads to a more severe disease progression. Also, as for adult EGPA, induction and maintenance of remission, and reduction in the requirement for long-term corticosteroid use are key treatment goals and are likewise key targets in the evaluation of an agent for the treatment of paediatric EGPA.

6.1.3. Mepolizumab in EGPA

Eosinophilia is central to the pathogenesis of EGPA, and IL-5 is a key cytokine regulating the life cycle of the eosinophil. Neutralization of IL-5 with mepolizumab therefore offers a potential therapeutic option for EGPA.

Mepolizumab (NUCALA), a humanised monoclonal antibody (IgG1, kappa, mAb), binds with high specificity and affinity to IL-5, the key cytokine responsible for regulation of blood and tissue eosinophils. The clinical program to support the indication for use of mepolizumab in patients with EGPA consists primarily of a single, Phase III study in adults. The study comprised a 52-week study treatment period and an 8-week follow-up period [Wechsler, 2017]. Due to the very low incidence and prevalence of EGPA in the paediatric population, a clinical trial was not considered feasible to support the paediatric indication. In this context, only individual case reports about the use of mepolizumab have been reported in paediatric patients aged 6 to 17 years [Joseph, 2018; Nara, 2019; Awouters, 2021].

6.2. Rationale

As a clinical programme for paediatric EGPA was not considered feasible, a paediatric investigation plan (PIP) was agreed by the Paediatric Committee (PDCO) which relies on a full extrapolation approach (PIP EMEA-000069-PIP04-13-M02). GSK submitted a Type II variation in October 2020 to EMA for the treatment of EGPA with mepolizumab in patients aged 6 years and above. GSK previously extrapolated from the adult EGPA population and applied trial results to the paediatric population.

To address a request from EMA's CHMP to generate data for mepolizumab in the post-marketing setting in paediatric patients aged 6 to 17 years in Europe, this study aims to

collect information on the real-world safety and effectiveness in paediatric EGPA patients treated with mepolizumab from sites across Europe in a case-series.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The purpose of this multinational, multi-site, case-series is to describe the real-world safety and effectiveness in individual paediatric EGPA patients treated with mepolizumab in Europe. Given the ultra-rare nature of the disease, a comparison group of EGPA patients who are not treated with mepolizumab will not be included in this study and no formal hypotheses will be tested. This study will focus on the occurrence of adverse events and change in OCS dosage after initiating mepolizumab.

7.1. Primary Objective

The **primary objective** of this study is to describe the real-world safety of mepolizumab treatment in paediatric EGPA patients aged 6 to 17 years in terms of AEs, SAEs, pregnancy exposures and medical device incidents.

7.2. Secondary Objectives

The **secondary objectives** of this study are:

- To describe the real-world effectiveness of mepolizumab treatment in terms of the effect of mepolizumab on OCS dosage
- To describe paediatric EGPA patients treated with mepolizumab per routine clinical care in terms of demographics, clinical characteristics, medical and treatment history.

8. RESEARCH METHODS

8.1. Study Design

This multinational, multi-site, case-series will aim to collect data on real-world safety and effectiveness up to 24 months after the initiation of mepolizumab treatment in paediatric EGPA patients in Europe. In addition, demographic and relevant medical history data will be collected up to 12 months prior to the first dose of mepolizumab.

EGPA in a paediatric population is extremely rare, and there will be challenges in identifying and recruiting eligible patients. The study design reflects these challenges. All eligible paediatric EGPA patients aged 6-17 years who initiated mepolizumab in the 12 months prior to the enrolment start date (regardless of whether they continue treatment following study enrolment or not), or who will initiate mepolizumab treatment at or after the enrolment start date will be invited for study enrolment by their treating physicians. These physicians will be from specialised centres and hospitals known to treat paediatric EGPA patients from selected countries in Europe. As the study is non-interventional, the decision to treat paediatric EGPA patients with mepolizumab will be made prior to and

independent from the decision to enrol patients into the study, and baseline and follow-up assessments will be in accordance with local standard medical care.

Per the local regulatory requirements, informed consent for minors (defined by the country law) will be obtained from the parent/caregiver with confirmation (assent) from the minor that he/she wishes to participate before enrolment into the study.

After obtaining informed consent from parents/caregivers and assent from paediatric patients, they will be enrolled into the study and data will be extracted from medical records and entered in an eCRF, where applicable.

Depending on the time point of the initiation of mepolizumab treatment in relation to the enrolment start date (i.e., the study start date), data for the primary and secondary objectives will be collected either prospectively (primary analysis) and/or retrospectively (supplemental analysis).

At enrolment, data from medical records before the initiation of mepolizumab treatment will be collected. These data will include available demographic and relevant medical history up to 12 months prior to the first dose of mepolizumab. Mepolizumab treatment information (e.g., dose and duration), safety data (AEs, SAEs, pregnancy exposures and medical device incidents) and effectiveness data (i.e., the effect of mepolizumab on OCS dosage) will be extracted from medical records from the first dose of mepolizumab until the end of follow-up. Patients will be followed for a maximum of 24 months after the first dose of mepolizumab, or until study discontinuation for any reason, or up to 12 months after mepolizumab treatment discontinuation; whichever comes first.

Subjects that permanently stop mepolizumab are not required to withdraw from the study. If for any reason a subject permanently stops mepolizumab, every effort should be made by the Investigator to keep the subject in the study to collect important safety and effectiveness data up to 12 months after mepolizumab treatment discontinuation.

In addition to the data extraction specified above, after the last study visit within routine care of each patient, physicians will provide a narrative/opinion on the benefit/risk profile of mepolizumab.

The Investigator or their designee will collect AE, SAE and medical device incident information until the AE, SAE or medical device incident is resolved or stabilised, or until the last study visit within routine care; whichever comes first. Pregnancies will be followed up to determine outcome (including premature termination).

The Investigator or their designee will extract data from medical records at routine care (scheduled and unscheduled) visits with their physician as they occur. Patients who are not seen for a period of 6 months will be contacted directly by the Investigator or their designee to collect minimal patient safety information, provided that this contact is considered by their physician to be within the standard of care for this patient.

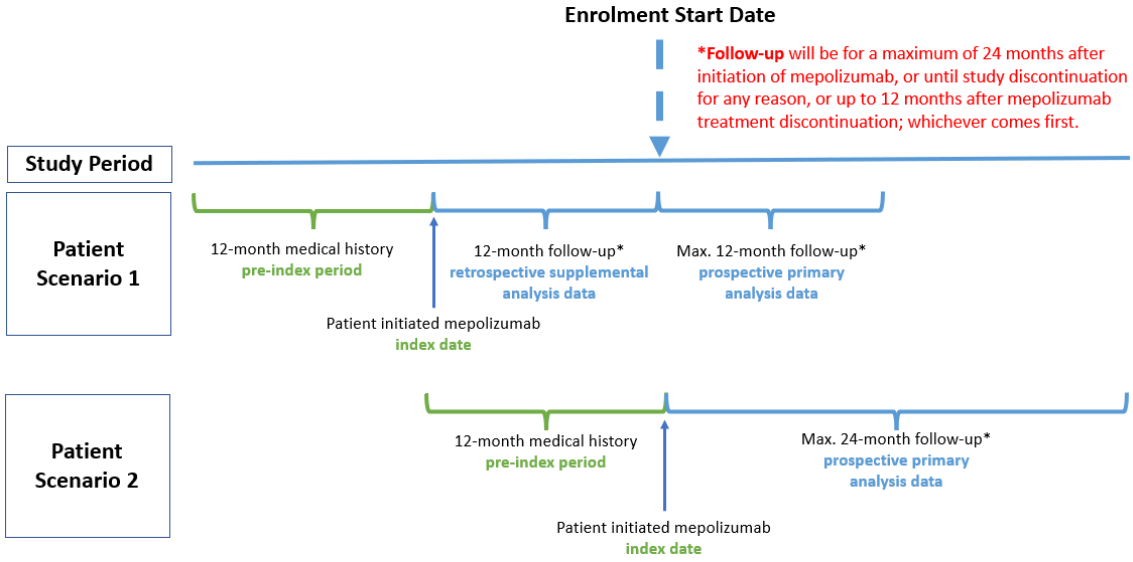
8.1.1. Definitions

The following definitions apply to the design of the study:

- ***Index date*** is defined as the date of the first (non-missing) dose of mepolizumab.
- The ***pre-index period*** for data collection is defined as up to 12 months prior to the index date.
- ***Study period is up to 36 months.*** It spans from 12 months before the index date, i.e., for collecting available demographic and relevant medical history prior to the first dose of mepolizumab until the end of the follow-up period.
- ***Follow-up period is up to a maximum of 24 months***. Depending on the time point of initiating mepolizumab treatment in relation to the enrolment start date, data will be collected either prospectively and/or retrospectively until 24 months after the index date, or study discontinuation for any reason, or up to 12 months after mepolizumab treatment discontinuation; whichever comes first.

Figure 1 shows the study workflow scenarios in detail for patients who initiated mepolizumab prior to or at enrolment.

Figure 1 Study Workflow Patient Scenarios



8.2. Study Population and Setting

It is planned to include all evaluable paediatric EGPA patients aged 6-17 years who already initiated mepolizumab treatment in the 12 months prior to the enrolment start date or who will initiate mepolizumab treatment after enrolment start date as part of routine clinical care from specialised centres and hospitals known to treat paediatric EGPA patients in Europe. **Note:** The primary analysis will include data for the primary and secondary objectives that are collected prospectively from patients who initiated mepolizumab at or after enrolment start date. The supplement analysis will include data for the primary and secondary objectives that are collected retrospectively for patients who initiated mepolizumab up to 12 months prior to the enrolment start date.

Once the treatment decision has been made, independent from the decision to enrol patients into the study, eligible paediatric EGPA patients will be invited for enrolment by treating physicians affiliated with Investigator sites participating in this study.

The proposed study enrolment period is 5 years, and it is estimated that approximately 10 evaluable paediatric EGPA patients will be enrolled. The feasibility of recruiting 10 patients within the 5-year time period will be evaluated annually. It is planned to follow patients for 24 months after the first dose of mepolizumab.

The total study duration is estimated to be a maximum of 7 years based on a planned study enrolment period of 5 years and a follow-up period of 24 months after the first dose of mepolizumab.

8.2.1. Inclusion Criteria

A patient who meets **all** of the following criteria is eligible for inclusion:

- Written informed assent and parent/caregiver consent
- Male or female, aged 6 to 17 years at the start of mepolizumab treatment
- Confirmed diagnosis of EGPA
- Initiated mepolizumab up to 12 months prior to enrolment start date (regardless of whether they continue treatment following study enrolment or not) or scheduled to receive treatment with mepolizumab at or after enrolment per routine clinical care

8.2.2. Exclusion criteria

A patient who meets **any** of the following criteria is not eligible for inclusion:

- Concurrent enrolment and/or participation in an interventional clinical trial involving either an investigational medicinal product or medical device
- Received treatment with mepolizumab more than 12 months prior to enrolment start date
- Received other biologics within 3 months of the first dose of mepolizumab.

8.3. Variables

8.3.1. Definitions

The following definitions apply to data collection:

- **Treatment discontinuation** is defined as a recorded clinician decision (with an associated decision date) to permanently discontinue mepolizumab treatment.
- **Treatment interruption** is defined as withholding ≥1 mepolizumab dose for any reason without a confirmed clinician decision to permanently discontinue treatment or initiate a new line of treatment.
- **Treatment delay** is defined as a delay (intentionally or unintentionally) in receiving mepolizumab without skipping a dose.

8.3.2. Baseline Characteristics

Baseline characteristic data at the date of the first mepolizumab dose (i.e., the index date) or up to 12 months prior to the first mepolizumab dose (i.e., the pre-index period) will be extracted if available from routine care visits at study enrolment.

The following data will be recorded where available:

- Demographics:
  - Age (at diagnosis, at mepolizumab initiation and at enrolment)
  - Sex
  - Race/ethnicity
  - Height/weight at mepolizumab initiation
- Clinical characteristics at diagnosis (most recent data available up to 12 months before or at diagnosis):
  - EGPA disease characteristics
    - Asthma with eosinophilia
    - Neuropathy
    - Pulmonary infiltrates
    - Sinonasal abnormality
    - Cardiomyopathy
    - Palpable purpura
  - ANCA-positive status
- Clinical characteristics at the index date (most recent data available up to 12 months before or at initiation of mepolizumab):
  - Absolute eosinophil count
  - EGPA disease status (remission, relapsing, refractory) according to European League Against Rheumatism (EULAR) criteria [Hellmich, 2007], if feasible, or to local standard practice
  - EGPA disease features based on the Chapel Hill Consensus Conference (CHCC) 2012 nomenclature system [Jennette, 2013]
  - Comorbidities at the index date (most recent data available up to 12 months before or at the index date)
- Treatment history regarding EGPA disease management (specifically OCS and immunosuppressants) and concomitant medications 12 months prior to the index date: type(s), start date(s), dose(s) and formulation(s)
- Additional variables to extract, if data is available:
  - EGPA American College of Rheumatology (ACR)/Lanham criteria at diagnosis
  - Asthma exacerbations prior to the index date defined as exacerbations of bronchial asthma which require hospitalisation, an emergency room visit or use of systemic steroids (any increase in dose that are higher than the maintenance OCS dose)
  - PVAS and PVDI score at the index date
  - Spirometry measurement results (FEV1) at the index date (most recent data available up to 12 months before or at the index date)
  - Hospital admissions at the index date (number, length of stay, primary reason for hospitalisation, ward type[s])

The World Health Organization (WHO) Drug Dictionary for medications will be used for coding drugs. The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding concomitant diseases.

8.3.3. Mepolizumab Treatment, Comorbidities and Concomitant Medications

Mepolizumab, comorbidities and concomitant medication data during the follow-up period will be extracted from medical records from routine care visits before or after enrolment depending on when a patient initiated mepolizumab.

The following data will be recorded where available:

- Mepolizumab treatment details:
  - Dates of administration
  - Dose
  - Formulation
  - Treatment setting (e.g., in-clinic, at home)
  - Reason for initiation of mepolizumab
  - Treatment changes (dose delays/interruptions, dose changes, discontinuation) and reasons
- Concomitant Medications (OCS, immunosuppressant and other):
  - Dates of administration
  - Dose
  - Formulation
  - Reason for initiation
  - Treatment changes (dose changes, discontinuation) and reasons
- Comorbidities during follow-up

8.3.4. Safety

8.3.4.1. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of AEs, SAEs, pregnancy exposures, adverse drug reactions (ADRs) and medical device incidents (including malfunctions) can be found in Section 10.1.

All AEs, SAEs, pregnancy exposures and medical device incidents that occur during and/or after administration of mepolizumab, regardless of a causal relationship to mepolizumab, will be recorded (coded using the MedDRA classification) in the eCRF. This will include recording information on seriousness, severity, action taken (with AE-related drugs coded using the WHO Drug Dictionary), and relationship to mepolizumab.

For AEs/SAEs, investigators will also need record in the eCRF if the event was related to a GSK product other than mepolizumab; details of the GSK product will be recorded in the Concomitant Medications page of the eCRF.

Medical device incidents related to mepolizumab will be recorded on the Medical Device Incident Form (Section 10.3).

Safety data during the follow-up period will be extracted from medical records from routine care visits before or after enrolment depending on when a patient initiated

mepolizumab. Timelines for reporting safety events during prospective follow-up (i.e., from enrolment until the end of follow-up) can be found in Section 10.3.

If an event is observed that is considered related to a drug product from another Sponsor (i.e., not GSK), the Investigator is advised to report the event to the appropriate marketing authorization holder of the suspected medicinal product or to the concerned competent authority via the national spontaneous reporting system.

8.3.4.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) include the following and these events will be subject to additional data collection within AE / SAE forms within the eCRF.

- Systemic reactions including anaphylaxis

Note: these events will be assessed by the Investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006] (See Section 10.2).

- Local injection site reactions

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

The Investigator or their designee will collect AE, SAE, pregnancy exposures and medical device incident information during the follow-up period.

All SAEs occurring at or after patient enrolment will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will send data to GSK within 24 hours of it being available. Safety data extracted retrospectively up to enrolment from patients who initiated mepolizumab up to 12 months prior to enrolment will be summarised in study reports only.

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 patient 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.

8.3.4.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs, SAEs and medical device incidents (as defined in Section 10.1) will be followed until the event is resolved or stabilised, or until the last study visit within routine care; whichever comes first.

8.3.4.5. Pregnancy

Details of all pregnancies in female patients will be extracted during the follow-up period. There is no requirement to collect pregnancy information from female partners of male patients.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons is required to 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.

Timelines for reporting pregnancies from enrolment until the end of follow-up can be found in Section 10.3. Pregnancy data collected up to enrolment from patients who initiated mepolizumab up to 12 months prior to enrolment will be summarised in study reports only.

The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the Sponsor. Any post-study pregnancy-related SAE considered reasonably related to a GSK product by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

8.3.4.6. Medical Device Incidents (Including Malfunctions)

Mepolizumab solutions are delivered via medicine/medical device combination products (pre-filled syringe/pen/auto injector). 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.

The definition of a medical device incident can be found in Section 10.1. **Note**: deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.2 and Section 10.3of the protocol.

Timelines for reporting medical device incidents from enrolment until the end of follow-up can be found in Section 10.3. Medical device incidents collected prior to enrolment from patients who initiated mepolizumab up to 12 months prior to enrolment will be summarised in study reports only.

8.3.5. Physician Narrative/Opinion

Physicians will provide a narrative/opinion on the benefit/risk profile of mepolizumab after the last study visit within routine care of each patient.

8.3.6. Additional Variables

The following variables assessed during the follow-up period will also be extracted from medical records from routine care visits before or after enrolment depending on when a patient initiated mepolizumab, if data is available:

- EGPA disease features based on the CHCC 2012 nomenclature system [Jennette, 2013] including respiratory and cardiac involvement during follow-up
- Absolute eosinophil counts
- EGPA disease status (remission, relapse or refractory) compared to previous visit according to EULAR criteria [Hellmich, 2007], if feasible, or to local standard practice
- Asthma exacerbations since last routine care visit defined as exacerbations of bronchial asthma which require hospitalisation, an emergency room visit or use of systemic steroids
- PVAS and PVDI scores recorded during follow-up
- Spirometry measurement (FEV1) recorded during follow-up
- Hospital admissions during follow-up
    - Admission and discharge date(s) since last routine care visit
    - Primary reason for hospitalisation

The PVAS is a 10-item, validated, clinician-completed tool used for the assessment of disease activity in systemic vasculitis divided into organ-based systems, with each section including symptoms/signs that are typical of that particular organ involvement in systemic vasculitis [Dolezalova, 2013]. Scores range from 0 to 63, depending on the existence or absence of clinical items for active vasculitis after excluding other causes (such as infection). The higher the score, the stronger the disease activity, with >5 points indicating vasculitis activity and ≥25 points indicating a high activity. Where available, PVAS scores will be extracted into the CRF.

The PVDI is a 72-item clinician-completed tool (not validated yet) to assess vasculitis damage defined as the presence of irreversible features present for at least 3 months since the onset of vasculitis [Dolezalova, 2014]. Where available, the total PVDI score will be extracted into the CRF.

8.3.7. Timings of Assessment

Available data will be extracted from medical records from patients' visits per routine clinical care into the eCRF (Table 1). In addition, after the last study visit within routine care of each patient, physicians will provide a narrative/opinion on the benefit/risk profile of mepolizumab.

Table 1 Data Collection Plan for Core Variables

Variables	**Pre-index period (12 months up to index date)**	**Index Date***	**Routine Care Visits****
Informed Assent and Parent/Caregiver Consent	X		
Patient Eligibility	X		
Demographics	X		
EGPA/Treatment History	X		
Comorbidities/Concomitant Medications	X		X
Mepolizumab Treatment		X	X
Safety (AEs, SAEs, pregnancy exposures, medical device incidents)		X	X
Physician narrative/opinion on the benefit/risk profile of mepolizumab			X[#]
Additional variables to extract, if data is available: respiratory/cardiac involvement, absolute eosinophil counts, EGPA disease status, asthma exacerbations, PVAS, PVDI, spirometry results, hospital admissions	X	X	X

Abbreviations: AE=adverse event; EGPA=eosinophilic granulomatosis with polyangiitis; PVAS= Paediatric Vasculitis Activity Score; PVDI=Paediatric Vasculitis Damage Index; SAE=serious adverse event.

*Index date is defined as the date of the first dose of mepolizumab.

**Data will be extracted only if recorded as part of routine care visits.

[#]This will be drafted based on information extracted per this Table from routine care visits after the last study visit within routine care of each patient.

8.4. Data Sources

Clinical data of paediatric EGPA patients enrolled into this study from sites in selected countries across Europe will be extracted by Investigators or their designees. Given the ultra-rare nature of the condition and specialist knowledge needed for diagnosis and treatment, the most populous countries within Europe will be selected and sites within countries will be selected based on their EGPA expertise, i.e., specialised centres and

hospitals known to treat paediatric EGPA patients from the literature, and their catchment area. All data elements will be extracted from information routinely recorded in medical records into the eCRF by the Investigator or their designee for the purposes of the study. Where required, patient/guardian self-report, hospital discharge summaries or other relevant healthcare records will be requested by the investigator or site staff for all SAEs among enrolled patients. In addition, physicians will provide a narrative/opinion on the benefit/risk profile of mepolizumab.

8.5. Study Size

The sample size is not based on statistical power consideration but on an estimate based on a previous feasibility assessment performed by GSK and a literature review in PubMed. Based on existing patient registries, healthcare databases, published case-series [Mossberg, 2018; Iudici, 2015; Eleftheriou, 2016; Fina, 2018; Gendelman, 2013; GSK, data on file] and consultations with a paediatric rheumatologist expert, at most 13 paediatric EGPA patients may be identified across the participating sites from selected European countries in five years of whom about 10 patients might be prescribed mepolizumab and willing to participate. The feasibility of the study will be evaluated on an annual basis. Analyses for this study will be descriptive as the sample size will be insufficient to perform statistical tests.

8.6. Data Management

All information outlined in Section 8.3 will be extracted into the eCRF from medical records. In addition, physicians will provide a narrative/opinion on the benefit/risk profile of mepolizumab.

Data collection will be completed in a suitable electronic data capture (EDC) platform. All data extracted will be stored at secure servers ensuring compliance with local or national regulations. Database lock is anticipated on the date the study is closed, i.e., when all documents and data have been collected, and reviewed and necessary data changes have been made after the last study visit within routine care for the last patient. Additional details regarding data collection and validation procedures will be detailed in a data management plan.

The investigator is responsible for ensuring data is entered in a timely manner and verifying that data are accurate and correct. When the study is completed, the investigators must retain essential documents, e.g., source data that support information entered in the eCRF, for as long as needed to comply with regulatory guidelines and Sponsor requirements. The investigator must permit study-related monitoring, audits, institutional review board (IRB) review, and regulatory agency inspections and provide direct access to source data documents. The investigator will notify the Sponsor prior to moving or destroying any of the study documents. 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.

8.7. Data Analysis

Data from this study will be described per patient as a case series, as the sample size will be insufficient to perform statistical analyses or summarise across patients.

8.7.1. Analysis Populations

8.7.1.1. Enrolled Population (EP)

The EP will consist of all patients for whom written informed assent as well as written informed consent from parents/caregivers has been obtained. The EP will be used to assess reasons for not initiating mepolizumab while being scheduled to initiate mepolizumab after enrolment.

8.7.1.2. Safety Population (SP)

The SP will include all patients in the EP who received at least one dose of mepolizumab. The SP will be the analysis population for descriptive, safety and effectiveness endpoints.

8.7.2. Statistical Methods

Given the ultra-rare nature of the disease, it is impractical to include a comparison group of EGPA patients who are not treated with mepolizumab in this study and so no formal hypotheses will be tested.

The primary analysis will present case reports of patients who initiated mepolizumab treatment at or after the enrolment start date. The primary analysis of prospective data will be supplemented with patients that had started mepolizumab prior to the enrolment start date (retrospective data) and will be presented separately.

8.7.2.1. Descriptive Analysis

Extracted data will be described per SP patient according to whether follow-up data was extracted before (retrospective) or after (prospective) enrolment. No further stratification will be conducted due to the small sample size. Missing data will not be imputed.

8.7.2.2. Analysis of Primary Objective

The primary objective for the study is to describe the real-world safety of mepolizumab treatment in paediatric EGPA patients during the follow-up period (see Section 8.3.1).

The following safety data will be described per SP patient according to whether follow-up data was extracted before (retrospective) or after (prospective) enrolment:

- AEs, SAEs and medical device incidents, and the corresponding number of events during the follow-up period; described by System Organ Class (SOC) and Preferred Term (PT) terms (MedDRA classification) as well as severity, seriousness, relationship to mepolizumab and outcome.
- All pregnancies during the follow-up period will be described.

8.7.2.3. Analysis of Secondary Objectives

The secondary objective for the study is to characterise paediatric EGPA patients treated with mepolizumab per routine clinical care in terms of demographics, clinical characteristics, medical and treatment history as well as real-world effectiveness of mepolizumab treatment in terms of the effect of mepolizumab on OCS dosage.

The following data will be described per SP patient **during the pre-index period**:

- Age (years) at diagnosis, mepolizumab initiation and enrolment
- Sex
- Ethnicity/Race
- Details of EGPA (symptoms and severity) at diagnosis, and at initiation of mepolizumab (EGPA status and duration of EGPA)
- EGPA management and concomitant medications (past 12 months)
- Absolute eosinophil count
- Comorbidities
- Additional variables to be described, if data is available:
  - EGPA American College of Rheumatology (ACR)/Lanham criteria at diagnosis
  - Number of asthma exacerbations (past 12 months)
  - PVAS and PVDI score at the index date
  - Baseline spirometry measurements (FEV1)
  - Number of hospital admissions (past 12 months) and length of stay

The following data will be described per SP patient according to whether follow-up data was extracted before (retrospective) or after (prospective) enrolment **during the post-index period**:

- Treatment data:
  - Mepolizumab treatment dose, duration of treatment (DoT), setting, formulation and (reasons for) discontinuation, dose delays/interruptions and dose changes
  - Daily OCS dose, DoT per formulation and (reasons for) discontinuation and dose changes
  - Immunosuppressant dose and DoT per type and formulation and (reasons for) discontinuation and dose changes
  - Other treatment type(s), dose(s), DoT and formulation(s)
- Physician narrative/opinion on the benefit/risk profile of mepolizumab including:
  - Comprehensive assessment of mepolizumab effectiveness as “effective”, “not effective” or “indeterminable” (including reasons) during the post-index treatment period (see definition Section 8.3.1).
- Additional outcomes to be described, if data is available:
  - Respiratory and cardiac involvement during follow-up
  - Absolute eosinophil counts (% change of baseline)
  - EGPA disease status (remission, relapse or refractory) during follow-up
  - Change from baseline in asthma exacerbations
  - Change from baseline in PVAS and PVDI
  - Change from baseline in spirometry measurement (FEV1).
  - Annual hospital admissions
  - Cumulative hospital admission length of stay

8.8. Quality Control and Quality Assurance

To ensure compliance with all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. See Section 8.8.5 for more details regarding the audit process.

8.8.1. Data Quality Assurance

Syneos Health and GSK are responsible for following standard operating procedures (SOPs) to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data. All sites will be trained by the Site Management Associate (SMA) on the protocol, study logistics, and the EDC system. Investigators will be reminded of the processes and importance of reporting all safety events (AEs, SAEs, pregnancy exposures and medical device incidents) and other information.

Data collection during this study will be managed using a software tool designed to ensure quality assurance and facilitate data capture during clinical studies. The investigator is responsible for ensuring prospective data is entered in a timely manner and verifying that data are accurate and correct by physically or electronically signing the eCRF.

On-line logic checks will be built into the EDC system as much as possible, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to the clinical study centre and answered electronically by that study centre's personnel.

This study will be conducted according to GSK SOP52213 (Conducting Quality Control Review of Study Results generated using Existing Data in Value, Evidence and Outcomes [VEO] and US VEO). This procedure requires documented evidence that the study protocol has been correctly interpreted and executed.

An independent QC analyst will document their review of the work of the Project Analyst. Analysts will reach and document agreement that the study results are complete, internally consistent, and accurately reflect the source data and intended purpose of this protocol.

8.8.2. Access to Source Data/Documents

The Investigator will allow Sponsor representatives, contract designees, authorised regulatory authority inspectors, and IRB to have direct access to all documents pertaining to the study.

8.8.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data extracted. All study materials will be returned to the Sponsor after the study has been completed.

Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations. According to International Council on Harmonisation (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

8.8.4. Study Monitoring

Participating sites will be queried every 12 months from study start to check for newly diagnosed paediatric EGPA patients who initiated treatment with mepolizumab in the previous 12 months.

Patient data will be monitored remotely. Monitoring visits may be scheduled throughout the study, if needed. Monitoring visits will be scheduled in advance, to ensure that the investigator has sufficient time to meet with the SMA and discuss all relevant findings. Patient data will be reviewed and/or audited, and all deficiencies corrected on site, if possible. A complete audit trail of all monitoring visits and data changes will be maintained. A virtual close-out visit will be scheduled when all documents and data have been collected, reviewed and necessary data changes have been made after the last study visit within routine care for the last patient. If the study is terminated, a virtual study close-out visit may be scheduled with the site if needed to retrieve all remaining study records. As long as COVID-19 restrictions apply, on-site study initiation and monitoring visits will not be scheduled until restrictions are alleviated.

The SMA will review the study conduct to determine compliance with the study protocol. The SMA will review and/or audit the electronic forms and source documents to ensure the accuracy and completeness of the data captured for the study. The SMA will review the informed patient assent and parent/caregiver consent forms (ICFs) to ensure that no forms were signed prior to the date of IRB approval of the study. The system for record-keeping will be reviewed.

8.8.5. Audits and Inspections

Responsible IRB/ Independent ethics committee (IEC)/Competent Authorities and/or the Sponsor’s clinical quality assurance group, or its designee, may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

8.9. Limitations of the Research Methods

8.9.1. Selection Bias

All eligible paediatric EGPA patients treated with mepolizumab from sites in Europe will be invited for study enrolment including patients who discontinued mepolizumab treatment before enrolment to reduce selection bias. Reasons for patient non-

participation, withdrawal or loss-to-follow-up will be recorded in the eCRF, if available, to address any remaining selection bias.

8.9.2. Information Bias

Relying on investigators to fill out the eCRF might induce the presence of missing data, which can result in bias. Entry of data in eCRFs will minimise missing or incorrect data by having automated queries. Clear instructions and engagement with the study staff, with appropriate training, as well as defining a core set of data to be extracted versus optional data (where available), will minimise the amount of missing data.

This study will collect follow-up data from medical records from patients before and after enrolment. Follow-up data recorded in medical records before patient enrolment may be of lesser quality with more missing data, and fewer details available than follow-up data collected after patient enrolment and thus after Investigators or their designees have been made aware of this study. For example, data recorded in medical records on adverse events may contain limited information before patient enrolment compared to after patient enrolment into this study. The primary analysis will present case reports of patients who started mepolizumab at or after enrolment. The primary analysis of prospective data will be supplemented with patients that had started mepolizumab prior to the study start date (retrospective data) and will be presented separately.

The anticipated small number of paediatric EGPA patients treated with mepolizumab included in this study and the lack of a comparison group of paediatric EGPA patients not treated with mepolizumab might limit the opportunity to draw any conclusions about the safety or effectiveness of mepolizumab treatment in this patient group. In addition, the anticipated heterogeneity of the population's clinical features and treatment history will limit generalisability of the study results.

8.9.3. Effect Modifiers

Effect modification occurs when the effects of a treatment vary by presence/level of another factor (effect modifier). Data will be described per SP patient according to whether follow-up data was extracted before or after enrolment. No further stratifications and effect modifier assessments will be conducted due to the small sample size.

8.9.4. Patients Lost to Follow-up or without Follow-up Data

Because the follow-up duration will be 24 months after the first dose of mepolizumab, the proportion of discontinued patients might be significant. Given the ultra-rare nature of the disease, additional patients will not be recruited to compensate for patients who discontinued the study before the end of follow-up at 24 months. Patients who are not seen for a period of 6 months will be contacted directly by the Investigator or their designee to collect minimal patient safety information, provided that this contact is considered by their physician to be within the standard of care for this patient. Reasons for loss-to-follow-up will be recorded in the eCRF if available.

8.9.5. Study Closure/Uninterpretability of Results

The planned study closure is Q4 2029 at the scheduled time of the final report of results. The end of study follow-up is projected to occur approximately 24 months following the inclusion of the last patient in the study. Annual interim reviews of study progress and patient numbers are planned to monitor feasibility.

The study can be terminated at any time for any reason by GSK in consultation with PRAC. The investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRB/IEC of the early termination of the study. The early termination of the study is considered a major amendment; therefore, the relevant competent authorities will be notified before a final decision is made and approval for termination is granted.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical Approval and Subject Consent

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (version 2008) and applicable legal and regulatory requirements and related guidances, especially Directive 2001/83/EC, Regulation (EC) No 726/2004 (REG) and Commission Implementing Regulation (EU) No 520/2012 (IR) as detailed in Good Pharmaco Vigilance Practices (GVP) Modules V, VI and VIII.

It is the responsibility of GSK and the Investigators to have prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., ICFs), if applicable, from the IRB/IEC/Competent Authorities. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF, or other study documentation.

Per the local regulatory requirements, informed consent for minors (defined by the country law) will be obtained from the parent/caregiver with confirmation (assent) from the minor that he/she wishes to participate before enrolment into the study. Each investigator will ensure that each patient is given full and adequate oral and written information in the local language about the nature and purpose of the study. The patient will be given the opportunity to ask questions and allowed time to consider the information provided. All parties will ensure protection of patient personal data and will not include names on any sponsor forms, reports, publications, or in any other disclosures, except where required by the local laws and regulations. The signed and dated informed parent/caregiver consent and patient assent forms must be obtained before any data is entered into the eCRF. The investigator must store the original, signed forms. A copy of the signed forms must be given to the patients and parents/caregivers. If the patient decides not to participate, the reason will be collected in the eCRF.

9.2. Subject Confidentiality

The informed parent/caregiver consent and patient assent forms will incorporate wording that complies with relevant data protection and privacy legislation in the participating country. Pursuant to this wording, patients will authorise the collection, use and disclosure of their personal data by the investigator and by those persons who need that information for the purposes of the study. The Sponsor and the Investigators will follow the EU General Data Protection Regulation that replaces the Data Protection Directive 95/46/EC and that was designed to harmonise data privacy laws across Europe, to protect and empower all EU citizens' data privacy, and to reshape the way organizations across the region approach data privacy.

The informed parent/caregiver consent and patient assent forms will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with the local law for data protection. The forms will also explain that for quality check or data verification purposes, a monitor of Syneos Health will require direct access to the signed parent/caregiver consent and patient assent forms or source documents that are part of the hospital or practice records relevant to the study.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Key Definitions

This study adopts the following ICH definitions:

Adverse event (AE): Any untoward medical occurrence in a patient, or clinical investigation subject, administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

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 Medicinal Product including those used in combination with a medical device. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e., lack of efficacy, with or without an adverse event), and adverse events associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse or those related to a deficiency occurring with a medical device or combination product.

Adverse (Drug) Reaction (ADR): A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Serious adverse event (SAE): Any untoward medical occurrence that at any dose that 1) results in death, 2) is life threatening, 3) requires inpatient hospitalisation or prolongs existing hospitalisation, 4) results in persistent or significant disability/incapacity or 5) is

a congenital anomaly. Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (ICH-E2D Guideline).

In general, hospitalisation signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. 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.

The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

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

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study entry even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of 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

- 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. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE

Events that do NOT meet the AE definition include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient'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 patient'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.

Pregnancy: Details of all pregnancies in female patients will be collected from the index date until the end of follow-up at 24 months after the first dose of mepolizumab, study discontinuation for any reason, or up to 12 months after mepolizumab treatment discontinuation; whichever comes first. There is no requirement to collect pregnancy information from female partners of male patients.
Pregnant patients will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on the patient and the neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons is required to be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age), still birth (occurring at > 22 weeks gestational age), congenital anomalies and ectopic pregnancies are always considered to be an SAE and will be reported as such.

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to mepolizumab by the Investigator, will be reported to GSK as described in Section 10.3. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Medical Device Incidents (including Malfunctions): Mepolizumab solutions are combination products comprising a medicine and a medical device:

- Mepolizumab subcutaneous injection Syringe: a pre-filled syringe filled with the medicinal solution of mepolizumab combined with a safety device.
- Mepolizumab subcutaneous injection Pen: a pre-filled syringe filled with the medicinal solution of mepolizumab combined with a pen-shaped inspirator.

When medical devices (Mepolizumab subcutaneous injection Syringe/Pen) are used, it may happen the malfunction (e.g., parts missing, device leaking, needle bent).

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other person or to a serious deterioration in his/her state of health.

Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An incident associated with a device happened and
- The incident was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Foetal distress, foetal death, or any congenital abnormality or birth defects.

Events that meet the medical device incident definition include but are not limited to:

- A patient, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse
- A patient's study intervention is interrupted or compromised by a medical device failure
- A misdiagnosis due to medical device failure leads to inappropriate treatment
- A patient's health deteriorates due to medical device failure.

Solicited events: Those adverse events related to the GSK product under evaluation and identified for collection as per study objectives.

Spontaneous events occurring during the study:
If an event is observed that is considered related to a drug product from another Sponsor (i.e., not GSK), the Investigator is advised to report the event to the appropriate marketing authorization holder of the suspected medicinal product or to the concerned competent authority via the national spontaneous reporting system.

Causality: The Investigator is obligated to assess the relationship between study participation and each occurrence of each AE/SAE. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study participation will be considered and investigated.

The Investigator will also consult the Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the Investigator must document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an AE/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 AE/SAE data to GSK.

The Investigator may change their opinion of causality in light of follow-up information and send an AE/SAE follow-up report with the updated causality assessment. The

causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.2. Collection of Adverse Events/Reactions

The purpose of the study is to monitor patients exposed to mepolizumab and to describe the safety profile in patients exposed to mepolizumab. For mepolizumab-exposed patients, all AEs, SAEs, pregnancy exposures and medical device incidents will be collected. These will be summarised in a final study report.

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 attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

The Investigator is obligated to perform or arrange for the review 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 as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations conducted as part of routine care, or consultation with other health care professionals. New or updated information will be recorded in the originally completed eCRF.

For AEs/SAEs, investigators will also need record in the eCRF if the event was related to a GSK product other than mepolizumab; details of the GSK product will be recorded in the Concomitant Medications page of the eCRF.

Severity and seriousness need to be independently assessed by the Investigator for each event recorded on the eCRF. The Investigator will make an assessment of severity (intensity) for each AE and SAE reported during the study and assign it to 1 of the following categories:

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

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

10.2.1. AEs of Special Interest

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

- Systemic reactions
- Local injection site reactions

Systemic reactions will be assessed by the Investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006]. The criteria do not make a distinction based on underlying mechanism and are summarised as follows:

1) Acute onset of an illness (minutes to several hours) 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:

    a) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

    b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

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

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

    b) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

    c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

    d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

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

    a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

    b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

10.2.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts (after the time of enrolment of the patient only). All SAEs and non-serious AEs of special interest will be followed until the event is resolved or stabilised, or until the last study visit within routine care; whichever comes first.

10.3. Reporting of Adverse Events/Reactions

All serious and non-serious AEs, pregnancy exposures, and medical device incidents occurring from patient enrolment until the end of follow-up will be collected and reported to the Sponsor's safety department. Safety follow-up data collected up to enrolment from patients who initiated mepolizumab up to 12 months prior to enrolment, will be summarised in study reports only.

All serious AEs, pregnancy exposures, and medical device incidents will be reported to the Sponsor within 24 hours of recognition. All non-serious AEs will be reported to the Sponsor within 5 calendar days of recognition. If a patient dies during participation in the study, the Investigator will provide GSK with a copy of any post-mortem findings including histopathology. The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information. The Investigator will submit any updated drug related AE data to GSK within 5 workdays of receipt of the information.

Investigators are not obligated to actively seek AE/SAEs after the conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and they consider the event to be reasonably related to mepolizumab, the Investigator must promptly notify the sponsor. As for death information, Investigator are asked to report it to the sponsor throughout the study period regardless of whether the death is related to mepolizumab or not. It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to GSK in lieu of completion of the GSK AE/SAE eCRF page. There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to GSK.

The Investigator must complete the Medical Device Incident Form for each patient who has a medical device incident. All of the header information in the form must be completed before sending to the sponsor. Original documents should be filed in the site study file. A copy of the form must also be sent to the study monitor. For medical device incidents fulfilling the definition of an AE or SAE, the appropriate pages of the eCRF must be completed. It is very important that the Investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. 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 an incident. This includes any amendment to the device design to prevent recurrence. If there is an SAE, the completed eCRF pages should be sent together with the Medical Device Incident Form. Device deficiencies will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device deficiency. The Medical Device Deficiency Report Form will be sent to the Sponsor by email. If email is unavailable, then fax should be utilised. The Sponsor will be the contact for the receipt of medical device deficiency reports.

The Investigator will collect pregnancy information on any female patient. The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the Sponsor. Any post-study pregnancy-related SAE considered reasonably related to a GSK product by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting. The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a patient's pregnancy. be withdrawn from the study. There is no requirement to collect pregnancy information from female partners of male patients.

The primary mechanism for reporting AE/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 in order to report the event within 24 hours, and the completed form can be sent to GSK by email (OAX37649@GSK.com) or facsimile (+44[0]20 8754 7822). Initial notification via email or facsimile does not replace the need for the Investigator to complete and sign the AE/SAE CRF pages within the designated reporting time frames. The site will enter the SAE data into the electronic system as soon as it becomes available. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new AE/SAE from a study patient or receives updated data on a previously reported AE/SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form.

A Safety Management Plan (SMP) will be developed for this study and will provide detailed information on the study specific pharmacovigilance processes and procedures including regulatory reporting requirements.

10.4. Safety Data Collection and Reporting Study Documentation

A SMP will be developed for the study and will provide detailed information on the study-specific pharmacovigilance processes and procedures to ensure a comprehensive approach to safety event collection, reconciliation, follow-up and reporting.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

GSK and/or a designated party will prepare safety and other summary reports, as required by the appropriate regulatory authority. In addition, these data may be summarised periodically for presentation at professional conferences and sessions, as appropriate.

GSK is responsible for presentations and/or publications. For studies that are fully or partially conducted by Investigator s who are not employees of the GSK group of companies, GSK and the Investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. GSK should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

In order to allow national competent authorities to review in advance the results and interpretations to be published, the Marketing Authorisation Holder will communicate to the Agency the final manuscript of the article within two weeks after first acceptance for publication.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Contact details of all Investigators participating in the study will be kept in a stand-alone document.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A post-authorisation safety study (PASS) to describe real-world safety and

effectiveness of NUCALA (mepolizumab) in paediatric eosinophilic granulomatosis with polyangiitis (EGPA) patients in Europe.

EU PAS Register number: Not registered yet.
Study reference number (if applicable):

Section 1: Milestones		**Yes**	**No**	**N/A**	**Section Number**
1.1	Does the protocol specify timelines for				
	1.1.1 Start of data collection[1]	☒	☐	☐	5
	1.1.2 End of data collection[2]	☒	☐	☐	5
	1.1.3 Progress report(s)	☒	☐	☐	5
	1.1.4 Interim report(s)	☐	☐	☒	
	1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5
	1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6.2/7
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
	2.1.2 The objective(s) of the study?	☒	☐	☐	7
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1/8.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.3

[1]Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.1/8.2/ 8.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.2
	4.2.2 Age and sex	☒	☐	☐	8.2.1
	4.2.3 Country of origin	☒	☐	☐	8.2
	4.2.4 Disease/indication	☒	☐	☐	8.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	8.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2/8.4

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.3.3

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7/8.7
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3/8.7
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.9.2
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.9.1
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9.2

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.9.3

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.1/8.2/ 8.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.1/8.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.1/8.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.3
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.3
	9.3.3 Covariates and other characteristics?	☒	☐	☐	8.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	8.7
10.4 Are stratified analyses included?	☒	☐	☐	8.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.7

Comments:

The sample size is not based on statistical power consideration but on an estimate based on a previous feasibility assessment performed by GSK and a literature review in PubMed.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	11

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: PPD

Date: 26/August/2022

Signature: PPD

Signature Page for 218065 TMF-14932952 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 23-Sep-2022 14:53:51 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 23-Sep-2022 15:02:07 GMT+0000

Reason for signing: Approved	Name: PPD Role: Author Date of signature: 23-Sep-2022 17:13:11 GMT+0000

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