NON-INTERVENTIONAL STUDY PROTOCOL

UNIQUE IDENTIFIER	213684
TITLE	A single arm, multi-center study to assess the long-term real-world safety and effectiveness of Nucala in EGPA patients who have already used Nucala for at least 96 weeks in Japan.
STUDY ACCOUNTABLE PERSON	PPD (Medical Japan)
CONTRIBUTING AUTHORS	Dr. PPD (Tohoku Univ.); Dr. PPD ; Dr PPD Dr. PPD ; Dr. PPD ; Dr. PPD ; PPD ; PPD ; PPD ; PPD ; PPD ; PPD

ASSET ID	SB240563
GSK ASSET	Mepolizumab (Nucala)
INDICATION	Eosinophilic granulomatosis with polyangiitis (EGPA)
PHASE OF DEVELOPMENT	n/a

REVISION CHRONOLOGY:

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15-JUN-2020	Original	N/A
27-JUL-2020	Amendment 01	• Addition of benefit/risk assessments • Addition of detailed description of each study period (screening period, observation period and follow-up period) • Change of time period for collecting AE • Change of Table for Schedule of activity • Removal of the opportunity of review by the identified investigator for the study reports • Change of a duration for retaining records and documents

SPONSOR SIGNATORY

PPD

PPD

Masaki Komatsubara

Date

Department Manager, Evidence Generation

Medical Japan

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ABBREVIATIONS

ADEs	Adverse device effects
ADRs	Adverse drug reactions
AEs	Adverse events
AESI	AEs of special interests
CCI [redacted]	[redacted]
ASE	All Subjects Enrolled
CCI [redacted]	[redacted]
CIOMS	Council for International Organizations of Medical Sciences
CROs	Contract Research Organisations
CCI [redacted]	[redacted]
DBF	Database freeze
DBR	Database release
eCRF	Electronic case report form
CCI [redacted]	
EGPA	Eosinophilic granulomatosis with polyangiitis
ENT	Ear, nose, and throat
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
GSK	GlaxoSmithKline
HCP	Healthcare Professional
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IHD	Individual human data
IL-5	Interleukin-5
MedDRA	Medical Dictionary for Regulatory Activities
MPO	Myeloperoxidase
MT	Malignant tumour
OCS	Oral corticosteroid
PDMP	Protocol Deviation Management Plan
PML	Progressive multifocal leukoencephalopathy
PMS	Post marketing surveillance
CCI [redacted]	[redacted]
RAP	Reporting and Analysis Plan
RCT	Randomized controlled trial
RMP	Risk management plan
SADEs	Serious adverse device effects
SAEs	Serious adverse events
SoA	Schedule of Activities
SRM	Study reference manual
sPVP	Study-specific pharmacovigilance plan
TP	Treated Population

CCI	[redacted]	[redacted]	

Trademark Information

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Nucala

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1. BACKGROUND AND RATIONALE

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as the Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small and medium sized blood vessels [Groh, 2005]. It is characterized by asthma, sinusitis, pulmonary infiltrates, neuropathy, and eosinophilic vasculitis of one or more organs [Jennette, 2013; Churg, 1951; Cottin, 2016; Guillevin, 1999].

Eosinophils contribute to the pathophysiology of EGPA by tissue and vascular infiltration and inflammation through different kinds of mediators [Akuthota, 2012; Khoury, 2014]. The cytokine interleukin-5 (IL-5) plays a crucial role in regulating the life cycle of eosinophils [Lopez, 1988; Rothenberg, 2006; Clutterbuck, 1989], and is found in very high levels in patients with EGPA [Hellmich, 2005]. Therefore, neutralization of IL-5 with mepolizumab, a humanized anti-IL5 monoclonal antibody, is a therapeutic option for EGPA [GlaxoSmithKline Document Number 2012N142276_03].

In Japan, 3401 patients with EGPA were certified as recipients of specific disease treatment [Japan Intractable Diseases Information Center, 2019]. According to a cross-sectional nationwide survey conducted by Sada et al., the prevalence of EGPA in Japan was estimated at 17.8 per 1,000,000 adults [Sada, 2014], which is similar to the prevalence reported in western countries (10.7-13 per 1,000,000 individuals) [Mahr, 2004; Martin, 1999]. In Japan, EGPA is one of the designated intractable diseases for promoting research to clarify the pathogenesis and to develop pharmaceutical products and medical devices, as well as to financially support patients with these diseases [Japan Intractable Diseases Information Centre, 2019].

Nucala (mepolizumab 300 mg, subcutaneous administration) was approved in Japan in 2018 for the treatment of EGPA in adult patients who inadequately respond to existing therapies [Nucala, 2020]. As the number of Japanese patients in clinical trials was limited, a Post marketing surveillance (PMS) study, special drug use investigation after its market launch, has been conducted in all patients administered Nucala for the treatment of EGPA in order to collect and assess information on the safety and effectiveness of the long-term use of Nucala in daily clinical practice in patients with EGPA [GlaxoSmithKline PMS protocol No. 208505]. However, the observation period of this PMS study is limited to up to 96 weeks (approximately 2 years) per patients from the start of Nucala administration. There have been no reports to date assessing the long-term safety and effectiveness of Nucala when used continuously beyond 96 weeks (approximately 2 years). There exists no-evidence not only in Japan, but also worldwide.

This study aims to assess the long-term safety and effectiveness of Nucala in the real-world setting in patients with EGPA who have already used Nucala for 96 weeks (approximately 2 years) after its market launch in Japan.

1.1. Benefit/Risk Assessment

1.1.1. Risk Assessment

This study does not involve the administration of any study treatment intervention to participants nor invasive study procedures. No potential risks beyond the routine clinical practice are considered in relate to participating in this study.

1.1.2. Benefit Assessment

By participating in this study, participants will be contributing to the understanding of long-term safety and efficacy of Nucala in a Japanese population, which may help provide a treatment option in the future.

1.1.3. Overall Benefit: Risk Conclusion

In the overall benefit-risk assessment, any risks that will affect the conduct of this study are not identified.

2. OBJECTIVES/ENDPOINTS

The objective of this study is to collect and assess information on the long-term (2 to 4 years) safety and effectiveness of Nucala (mepolizumab 300 mg, subcutaneous administration) in patients with EGPA, who have already used Nucala for 96 weeks (approximately 2 years), in real-world settings in Japan.

Objectives	Endpoints
Primary	
To investigate the long-term safety of Nucala in adult patients with EGPA	• Frequency of Adverse events (AEs)/ serious adverse events (SAEs) • Frequency of AEs related to Nucala (adverse drug reactions, ADRs) • Frequency of AEs of special interests (AESI)
Secondary	
To investigate the long-term effectiveness of Nucala in adult patients with EGPA	• Proportion of participants with clinical symptoms as assessed by 9 organ-systems (i.e. systemic, skin, mucous membranes/eyes, ears/nose/throat, chest, cardiovascular, abdominal, renal, nervous system) • Proportion of participants with EGPA relapse[a] • Annualized rate (event/year) of hospitalization for EGPA-related events • Annualized rate (event/year) of emergency

	room/unscheduled visit for EGPA-related events • Average daily dose (prednisolone-equivalent) of oral corticosteroid (OCS) over 96 weeks. • The proportion of subjects in the dosing categories* relative to average daily OCS (prednisolone-equivalent) over 96 weeks * Zero, >0 to ≤4.0 mg/day, >4.0 to ≤7.5 mg/day, >7.5 mg/day
Exploratory	
CCI [redacted]	

a. EGPA relapse is defined as any of the following with worsening EGPA. 1) Increased dose of OCS. 2) Initiation/increased dose of immuno-suppressive agents. 3) EGPA treatment with hospitalization (Section 4.6).
b. EGPA recurrence is judged by investigator based on the following definitions (only in participants who have been withdrawn from/terminated the Nucala treatment and entered the follow-up period due to symptom improvement per clinical judgement):1) Initiation/increased dose of OCS, 2) Initiation/increased dose of immuno-suppressive agents, 3) Hospitalization in association with the EGPA treatment (Section 3.4).

3. RESEARCH METHODOLOGY

3.1. Study Design

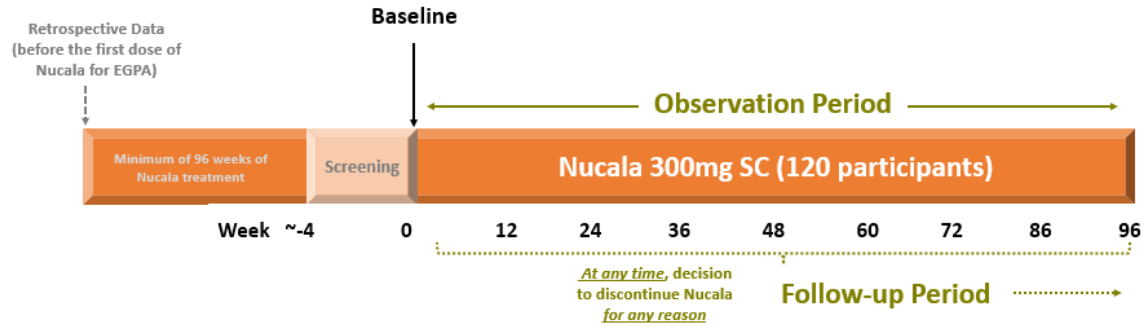
This is a single-arm, multi-center, prospective, non-interventional, observational study to assess the long-term (2 to 4 years) real-world safety and effectiveness of Nucala in adult patients with EGPA who have already received Nucala treatment for 96 weeks (approximately 2 years) after its market launch in Japan and who completed the Nucala

PMS study (special drug use investigation; Protocol No. 208505, NCT03557060). To reflect the real-world setting, inclusion and exclusion criteria as well as concomitant treatment criteria are limited to the minimum required. Approximately 120 participants will be enrolled in the study.

The primary objective is to investigate the long-term safety of Nucala, with special attention to AEs, AESI, and SAEs, in adult patients with EGPA in Japan. The effectiveness of Nucala will also be investigated as secondary and exploratory objectives. Endpoints for effectiveness are included in reference to endpoints in the PMS study.

The study schema is provided in Figure 1. The data in the routine clinical practice will be collected in the study.

Figure 1 Study Schema



This study is an observational study that does not involve the administration of study treatment intervention. According to the Japanese prescribing information for Nucala, 300 mg mepolizumab is injected subcutaneously every 4 weeks in adult patients with EGPA, who inadequately respond to other existing therapies. Participants receive marketed products of Nucala in any of the approved formulations; lyophilized products and/or liquid products (prefilled syringe/auto-injector pen).

This study is composed of three periods: screening period, observation period and follow-up period.

Screening period

During the screening period (0-4 weeks), all participants are assessed to determine whether they meet the eligibility criteria. Retrospective data are collected for reference regarding the clinical symptoms/findings and laboratory parameters before the first dose of Nucala (at least 96 weeks [approximately 2 years] before). These retrospective data should be from physician source/medication record. By using the retrospective data,

information could be provided about the change from pre-Nucala exposure to the end of this study, of which a period would be approximately 4 years.

Any participant who completes assessments during the screening period but does not continue in the study beyond Baseline or is subsequently found to be ineligible for the study prior to Baseline, is classified as Screen Failure. Information collected for the participant classified as Screen Failure is detailed in the guideline for eCRF entry. Re-screening is permitted once only.

Observation period

During the observation period, which is scheduled for 96 weeks (approximately 2 years) at maximum, safety and effectiveness data are obtained at approximately 12-week intervals. The intervals may be shorter/longer or may be irregular depending on the usual pattern of healthcare visits.

Any data collected during the observation period are entered into eCRF. The assessments in the routine clinical practice during the observation period are shown in Section 9.1 (Appendix 1).

Follow-up period

The follow-up period is only applicable to participants who have discontinued the treatment of Nucala due to any reason. The assessments in the routine clinical practice during the follow-up period are shown in Section 9.1 (Appendix 1).

In case EGPA symptoms are deteriorated in a participant who previously discontinued the treatment of Nucala due to improvement of EGPA symptoms, the participant can receive the re-treatment of Nucala during the follow-up period. The participant who received the re-treatment of Nucala continues the assessments in the follow-up period.

3.2. Data Source / Data Collection

CRF data

For this study, participant data will be entered into GlaxoSmithKline (GSK)-defined Electronic case report forms (eCRFs), transmitted electronically to GSK, and combined with data provided from other sources in a validated data system. Personal information such as “participant name”, “participant initial” and “full date of birth” will not be collected in eCRF, and each participant will be managed with Subject ID in eCRF and clinical database for anonymization.

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

eCRFs (including queries and audit trails) will be retained by GSK and copies will be provided to the investigator to be maintained. Participant initials will not be collected and transmitted to GSK according to a GSK policy.

3.3. Eligibility Criteria

3.3.1. Inclusion Criteria

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

1. Adult patients with EGPA of ≥20 years of age inclusive, at the time of signing the informed consent.
2. Participants must have a current clinical diagnosis of EGPA by physician.
3. Participants have continuously used Nucala for at least 96 weeks for the treatment of EGPA as mentioned in the current label in Japan.
    - Participants thus were registered and completed the Nucala PMS study (special drug use investigation; Protocol No. 208505, NCT03557060) prior to be enrolled in this study.
4. Physician's decision to continue treatment with Nucala for the treatment of EGPA as mentioned in the current label in Japan.
5. Prior to commencing any study related activities, participants must be able and willing to provide written informed consent.

3.3.2. Exclusion Criteria

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

1. Participants who have previously discontinued Nucala treatment for EGPA for more than 12 weeks.
2. Participating in another clinical trial within the past 12 months, in which the participant has been exposed to an investigational or non-investigational pharmaceutical product.
3. Participants with any reasons that in physician's opinion would place the patients at risk.
4. Participants who are pregnant or breastfeeding.

3.3.3. Withdrawal from Study

- A participant may withdraw from the study and stop reporting data at any time at his/her own or physician's request, or if they are lost to follow-up.
- To determine the safety and effectiveness of Nucala administration in participants who discontinued the treatment, a follow-up investigation (up to planned Week 96 of observation period) should be conducted wherever possible.
- If the participants enroll in another study involving investigational study treatment intervention while enrolled in this study, they will be withdrawn from the present study.

3.4. Variables

The investigator will collect information about the following variables wherever possible and record it on the eCRF. The timing of collecting information is listed in Section 9.1 (Appendix 1) (SoA).

- Demography: Age, sex, body weight, height, EGPA severity classification*, and medical history/comorbidity

*Defined by Japan Intractable Diseases Information Center (Japan Intractable Diseases Research Foundation)

- Administration status of Nucala for EGPA, including product formulation information
- Concomitant medications and therapies
- Adverse events, SAEs, and AESI *

*AESI: hypersensitivity (including anaphylaxis), infections and malignant tumors, defined as safety specifications in the Japanese RMP

- Clinical symptoms (only disease activities relevant to EGPA in systemic vasculitis assessed) of the following 9 organ systems [Sada, 2014]:

  1) Systemic
  2) Skin
  3) Mucous membranes/eyes
  4) Ear, nose and throat (ENT)
  5) Chest
  6) Cardiovascular

7) Abdominal

8) Renal

9) Nervous

- Hospitalization for EGPA-related events
- Emergency room/unscheduled visit for EGPA-related events
- Asthma exacerbation as defined below:

1) Exacerbation of bronchial asthma which requires hospitalization

2) Exacerbation of bronchial asthma which requires emergency room visit

3) Exacerbation of bronchial asthma which requires the use of systemic steroids*

*The standard definitions for the use of systemic steroids are as follows:

When a participant requires continuous administration of steroids systemically, in concrete terms, orally, intravenously or intramuscularly, for ≥3 days. However, as for intramuscular injection, it must also include a continuous administration of dexamethasone sodium phosphate or betamethasone sodium phosphate for ≥3 days, or one or more doses of triamcinolone acetonide.

When a participant receiving the maintenance therapy with systemic steroids requires doubling the maintenance dose for ≥ 3 days for exacerbation of bronchial asthma.

Exacerbations that occurred <7 days from the last exacerbation were treated as a continuation of the same exacerbation.

- Clinical laboratory parameters: CCI [redacted]
- Lung function: CCI [redacted] (with reason for examination of pulmonary function)

Pre- and post-bronchodilator values will be collected as respective separate categories. If it is not known whether the reading is pre- or post-bronchodilator, this will be collected as unknown.

- CCI [redacted]
- EGPA recurrence is judged by investigator based on the following definitions (only in participants who have been withdrawn from/terminated the Nucala treatment and entered the follow-up period due to symptom improvement per clinical judgement):

1) Initiation/increased dose of OCS

2) Initiation/increased dose of immuno-suppressive agents

3) Hospitalization in association with the EGPA treatment

Note that EGPA relapse is defined in Section 4.6.

3.5. Sample Size / Power Calculations

In a global Phase 3 study (MIRRA study) [Wechsler, 2017] conducted in EGPA patients (mepolizumab group: 68 patients), the minimum frequency of AEs was 1.47% (1/68 patients). Assuming a binominal distribution, 107 participants are required to detect at least one case of an AE occurring with the frequency of 1.5% or higher with the probability of 80%. With an expected dropout rate of 10%, a total of approximately 120 participants are needed as the safety analysis population.

A total of 80 and 153 participants are required to detect at least one case of an AE occurring with the frequency of 1.5% or higher with the probabilities of 70% and 90%, respectively.

No sample size re-estimation is planned.

4. DATA ANALYSIS CONSIDERATIONS

All pre-specified analyses will be described in a full Reporting and Analysis Plan (RAP) which will be finalized prior to database release (DBR).

This is a descriptive study. The study is not powered to detect differences and no formal statistical hypothesis testing will be performed for any of the endpoints.

4.1. Analysis Populations

The populations for analyses are defined as shown below.

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• All participants enrolled into the study meeting the eligibility criteria for the study.	• Study Population
Treated Population (TP)	• All participants in the ASE study population who have received at least 1 injection of	• Study Population • Safety • Efficacy

Population	Definition / Criteria	Analyses Evaluated
	Nucala.	

4.2. Protocol Deviations

- This study does not include a per protocol population.
- Important protocol deviations (including deviations related to study inclusion/exclusion criteria) will be summarised and listed.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP).
- Data will be reviewed prior to Database freeze (DBF) to ensure that important deviations (for inclusion in the Clinical Study Report) are identified and captured in the deviations dataset.
- The deviations dataset will be the basis for summaries and listings.

4.3. Summary of Patient Characteristics

Characteristics of enrolled participants collected at baseline will be described. This will include demographic information as well as disease characteristics. Results will be used to describe ASE population. This analysis is planned to be performed prior to and/or at the last participant first visit, depending on recruitment, and will not require formal statistical analysis. This analysis will not lead to a decision to amend the design or stop the study, and will be described further in the RAP.

4.4. Interim Analysis

The purpose of the interim analysis that for present results of the analysis for the primary outcome of the long-term safety of Nucala, and the secondary outcomes of the long-term effectiveness of Nucala using dataset including data until 48 weeks post-exposure. This analysis will not lead to a decision to amend the design or to stop the study.

The interim analysis will be based on the TP Population, and the prespecified analyses will be carried out using interim dataset.

All required database cleaning activities will be completed and interim DBR and DBF will be declared by Data Management.

4.5. Primary Analysis

The primary analysis will be based on the TP population. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by preferred terms. All AEs, SAEs, ADRs and AESIs will be summarized separately. Exposure-adjusted AE rate for these AE will also be summarized.

The summary table will be also produced by the observation period, the follow-up period and the total period (the observation period and the follow-up period), respectively.

4.6. Secondary and Exploratory Analyses

The secondary and exploratory analyses will be performed for the TP population. All endpoints will be summarised by using appropriate descriptive statistics.

The summary table will be also produced by the observation period and the follow-up period, respectively.

The endpoints selected for secondary and exploratory analyses are listed below by objective:

<u>To investigate the long-term effectiveness of Nucala in adult patients with EGPA in Japan</u>

- Proportion of participants with clinical symptoms as assessed by 9 organ-systems (i.e. systemic, skin, mucous membranes/eyes, ears/nose/throat, chest, cardiovascular, abdominal, renal, nervous system) for the observation period of 96 weeks.
- Proportion of participants with EGPA relapse for the observation period of 96 weeks.

  EGPA relapse is defined as any of the following with worsening EGPA.*

  1) Increased dose of OCS.

  2) Initiation/increased dose of immuno-suppressive agents.**

  3) EGPA treatment with hospitalization.

  * Worsening of EGPA: new onset of EGPA symptoms or worsening of existing symptoms.

  ** Immunosuppressive agents: If the dose of immunosuppressive agents increases for the same formulation or if the number of immunosuppressive agents increases for EGPA treatment.
- Annualized rate (event/year) of hospitalization for EGPA-related events

- Annualized rate (event/year) of emergency room/unscheduled visit for EGPA-related events

  The annualized rate of hospitalization for EGPA treatment will be analysed by using a negative binomial generalized linear model with logarithm of time as an offset variable, from which the estimated event per year and associated 95% CIs will be calculated.

- Average daily dose (prednisolone-equivalent) of OCS over 96 weeks

- The proportion of subjects in the dosing categories* relative to average daily OCS (prednisolone-equivalent) over 96 weeks

  * Zero, >0 to ≤4.0 mg/day, >4.0 to ≤7.5 mg/day, >7.5 mg/day

CCI

To investigate the maintenance of response after cessation of Nucala treatment

- Time to EGPA recurrence up to Week 96 in participants who discontinued/withdrew from Nucala treatment due to symptom improvement.

  Summaries and graphs of the Kaplan-Meier estimates of the proportion of participants with an EGPA recurrence over time will be produced. (Definition of EGPA recurrence: See Section 3.4).

To investigate the condition of complicated asthma

- Annualized rate (event/year) of asthma exacerbation.

  The annualized rate of asthma exacerbation will be analysed by using a negative binomial generalized linear model with logarithm of time as an offset variable, from which the estimated event per year and associated 95% CIs will be calculated.

To explore the effect on pulmonary function

CCI [redacted]

To explore the effect on the cardiac function

CCI [redacted]

The statistical model was selected with reference to previous clinical studies of Nucala. However, for a model checking and diagnostics, the fit of the negative binomial generalized linear model will be investigated by calculating standardized deviance residuals and plotting these on a "Q-Q" plot with simulation-generated tolerance boundaries, where appropriate.

Further details of the secondary and exploratory analyses including covariates will be provided in the RAP or the supplementary RAP, when needed.

4.7. Subgroup Analysis

The following subgroups are of interest in this study. A separate exploratory analysis of the prespecified endpoints within each subgroup will be carried out. Subgroup categories may be further collapsed if there are a small number of participants within a subgroup.

The following subgroups are of interest:

- Sex
- Age
- Duration of EGPA disease
- Severity of EGPA disease
- Adherence to recommended treatment regimen for Nucala
- Current medical conditions (e.g., presence/absence of asthma, allergic rhinitis, etc.)
- Medical history (e.g., presence/absence of asthma, allergic rhinitis, etc.)
- Prior use of Nucala for asthma

- Previous therapeutic regimen for EGPA disease (e.g., presence/absence of plasma exchange therapy, operation, etc.)
- Prior use of other biological medications
- ANCA
- Favourable treatment response with Nucala
- Immuno-suppressive therapy
- EGPA disease relapse
- Clinical symptoms
- COVID-19 infection

Further details of the subgroup analyses will be provided in the RAP.

5. LIMITATIONS

This observational study aims at assessing outcomes in usual clinical settings, thereby characterizing the real-world treatment safety and effectiveness of Nucala in patients with EGPA. Nonetheless, there may be limitations on the generalizability of study results. The patient recruitment to this study is biased toward those who have completed the PMS study prior to being enrolled in this study: the study enrolled only participants who have responded well to Nucala and experienced no AEs leading to treatment discontinuation. This may lead to a patient selection bias affecting estimates of the long-term safety and effectiveness of Nucala obtained from the study. It might be helpful to compare patient backgrounds in this study with those from the PMS study in order to consider selection bias.

In addition, given that the sample size was estimated based on the anticipated occurrence of AEs, the study is unlikely to produce sufficient data for the analyses of effectiveness. Therefore, it would be difficult to give a robust clinical interpretation regarding any of the Nucala treatment-related outcomes in patients with EGPA. Hence, caution should be observed when interpreting the results of this study.

6. STUDY CONDUCT, MANAGEMENT & ETHICS

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Ethical Guidelines for Medical and Health Research Involving Human Subjects;

- Applicable laws and regulations.

The protocol, protocol amendments, Informed consent form (ICF), and other relevant documents (e.g., advertisements) must be submitted to an Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IEC before the study is initiated.

Any amendments to the protocol will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC;
- Providing oversight of the conduct of the study at the site and adherence to requirements of the IEC, and all applicable regulations.

Other study oversight considerations (study conduct and management information) are provided in Section 9.2 (Appendix 2).

6.1. Legal Basis for Processing Individual Human Data

The authors confirm that study data is Individual Human Data (IHD) owned by GSK and that the proposed use of the IHD is **Study Use*** as outlined in the patient consent.

* Study Use means - the use of IHD is as stated in the original study protocol and/or aligned with the informed consent form to answer the study objectives and satisfy regulatory requirements and learn more about the Nucala studied and the disease/condition studied. This includes bringing the Nucala to market or maintaining market access which includes working with government agencies, insurers or health care payers and aiding GSK's understanding of clinical efficacy, safety, or effectiveness of the product.

6.2. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE are provided in Section 9.3 (Appendix 3).

The definitions of device-related safety events can be found in Section 9.5 (Appendix 5) (Device deficiencies are covered in Section 6.2.6).

The investigator and any qualified designees are responsible during the study for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, of special interest, or considered related to Nucala.

Participants will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

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

All AEs should be monitored throughout the study. All AEs and SAEs must be recorded in the eCRF.

All AEs and SAEs will be collected from the signing of the informed consent form until the final study visit.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours of recognition, as indicated in Section 9.3 (Appendix 3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. AEs related to Nucala will be recorded and reported to the sponsor or designee within 5 work days of recognition.

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 participant has been discharged from the study, and they consider the event to be reasonably related to Nucala, the investigator must promptly notify the sponsor. As for death information, investigators are asked to report it to the sponsor throughout the study period regardless of whether the death is related to Nucala or not.

6.2.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 9.3 (Appendix 3).
- Care will be taken not to introduce bias when detecting an AE and/or an SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about the occurrence of AE.

6.2.3. Follow-up of AEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, AEs related to Nucala and AESIs will

be followed until the event is resolved, stabilized, or otherwise explained, or the participant is lost to follow-up. Further information on follow up procedures is given in Section 9.3 (Appendix 3).

6.2.4. Regulatory Reporting Requirements for AEs and SAEs

Prompt notification by the investigator to the sponsor of AEs and SAEs are essential so that legal obligations and ethical responsibilities towards the safety of participants are met.

6.2.5. Pregnancy

No female participants who become pregnant while participating in the study are required to be withdrawn from the study.

Details of all pregnancies in female participants will be collected after obtaining informed consent and until the final study visit. There is no requirement to collect pregnancy information from female partners of male participants.

If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 9.4 (Appendix 4).

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

6.2.6. Medical Device Incidents (Including Malfunctions)

The Nucala solution are combination products comprising a medicine and a medical device.

The Nucala solutions are following;

- Nucala subcutaneous injection 100 mg Syringe: a pre-filled syringe filled with the medicinal solution of mepolizumab which combined with a safety device.

- Nucala subcutaneous injection 100 mg Pen: a pre-filled syringe filled with the medicinal solution of mepolizumab which combined with a pen-shaped inspirator.

In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device incident that occurs during the study with such devices.

The definition of a Medical Device Incident can be found in Section 9.5 (Appendix 5).

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 6.2.3 and Section 9.3 (Appendix 3) of the protocol.

6.2.6.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device incident at any time after a participant has been discharged from the study, and such a device incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting medical device incidents is provided in Section 9.5 (Appendix 5).

6.2.6.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE or SAE will be followed and reported in the same manner as for other AEs (see Section 6.2.3). Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

6.2.6.3. Prompt Reporting of Medical Device Incidents to Sponsor

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

6.2.6.4. Regulatory Reporting Requirements for Medical Device Incidents

- Prompt notification by the investigator to the sponsor of safety information relating to medical devices is essential so that legal obligations and ethical responsibilities towards the safety of participants are met.

6.2.6.5. Medical Device Malfunctions

- When medical devices (Nucala subcutaneous injection 100 mg Syringe/Pen) are used, it may happen the malfunction (e.g., parts missing, device leaking, needle bent). The information provided in this section applies to occurrence and reporting of device malfunctions that are NOT associated with an AE/SAE.
- Participants will be instructed to contact the investigator, when they experience a device malfunction.

6.3. Adverse Event (AE), Pregnancy Exposure, and Incident Reporting Related to Any GSK Product

All serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK product will be collected and reported as described in the study-specific pharmacovigilance plan (sPVP). The sPVP is provided in Section 9.6 (Appendix 6). This plan will include the following elements to ensure a comprehensive approach to safety event collection and reporting:

- Supplier pharmacovigilance training
- Investigator and site staff pharmacovigilance training
- Safety-specific roles
- AEs, pregnancy exposures, and incidents collection and reporting processes
- AE, pregnancy exposure, and incident collection forms
- Frequency of data review
- Reporting process and timelines
- Interim reports
- Reconciliation process
- Study-specific PVP monitoring process
- Provision of final study report

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Target audience

The information generated by this study will contribute to the published literature and provide Healthcare Professional (HCPs) with information about the use of Nucala in patients with EGPA. GSK stakeholders also have an interest in the information generated by this study. The results may be disseminated externally via manuscripts and/or presentations.

Interim analysis and reporting

Interim analysis will be performed as specified in Section 4.4, and the corresponding publications will be produced as necessary.

Final analyses and reporting

A final study report will be generated after the final analysis. The final report will encompass all planned analyses, including a description of the complete study population, as described in the RAP. The study protocol will be entered into the ClinicalTrials.gov.

Any publication of the results from this study will be consistent with GSK's publication policy and guided by the International Committee of Medical Journal Editors [International Committee of Medical Journal Editors, 2019].

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9. APPENDIX

9.1. APPENDIX 1: SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening		Observation period			Follow-up[1]
Time period for which data should be collected at usual EGPA healthcare visits, if this is possible	Up to 4 weeks before Week 0[2] (Screening[2])	(Retrospective data[3] collection)	Week 0 Baseline	Week 12 to 96; no more frequently than every 12 weeks (±4weeks)	Early withdrawal	Up to 96 weeks after Week 0
Informed consent	X[4]					
Inclusion and exclusion criteria	X					
Demography	X					
Administration status of Nucala for EGPA	X		X	X	X	X[5]
Concomitant medication	X	X[6]	X	X	X	X
Concomitant therapies	X	X[7]	X	X	X	X
Adverse events	X		←	———	———	→
Clinical symptoms		X	X	X	X	X
Hospitalization for EGPA-related events		X[8]	X	X	X	X
ER/Unscheduled visit for EGPA-related events		X[8]	X	X	X	X
Asthma exacerbation		X[8]	X	X	X	X
Clinical laboratory parameters[9], if performed		X	X	X	X	X
Lung function, if performed		X	X	X	X	X
Ejection fraction, if performed		X	X	X	X	X
Pregnancy reporting			←	———	→	
EGPA recurrence						X

1. The follow-up period is only applicable for participant who discontinued the treatment. If drug-related adverse events occurred, contact the sponsor.
2. Screening and Week 0 can occur on the same day.
3. Retrospective data within 12 weeks (otherwise specified) before the first dose of Nucala for EGPA.
4. Informed consent must be obtained prior to start of any study's procedure.
5. Only for in case of receiving the re-treatment of Nucala.
6. Only for other biological products, Nucala for asthma, corticosteroid, immunosuppressants, and immunoglobulin.
7. Only for EGPA therapies.
8. Number of events within 48 weeks before the first dose of Nucala for EGPA.
9. Haematological parameters tested are: CCI [redacted]

9.2. APPENDIX 2: STUDY OVERSIGHT CONSIDERATIONS

9.2.1. Informed Consent Process

The investigator or their representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of local regulations, where applicable, and the IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

9.2.2. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

9.2.3. Plans for Disseminating and Communicating Study Results

GSK will provide the investigator with the full summary of the study results.

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

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

9.2.4. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organisations [CROs]).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, Ethical Guidelines for Medical and Health Research Involving Human Subjects, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 10 years from the issue of the final Clinical Study Report (CSR) or equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

9.2.5. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. The definition of what constitutes source data will be found in the source data agreement.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

9.2.6. Study and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC or local health authorities, the sponsor's procedures, or Ethical Guidelines for Medical and Health Research Involving Human Subjects;
- Inadequate recruitment of participants by the investigator.

9.2.7. Publication Policy

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

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

9.3. APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.3.1. Definition of an AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with study participation, whether or not considered related to study participation. NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with study participation.
Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific 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 fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.3.2. Definition of an SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during 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.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

9.3.3. Recording and Follow-Up of AEs and SAEs

SAE Recording

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

Assessment of Intensity

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

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

Assessment of 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 Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that 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.

Follow-up of AEs and SAEs

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

9.3.4. Reporting of AE and SAE to GSK

AE and SAE Reporting to GSK via Electronic Data Collection Tool

- 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 (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new AE/SAE from a study participant 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 (see next section). • Contacts for AE/SAE reporting can be found in the SRM.
AE and SAE Reporting to GSK via Paper CRF
• Facsimile or email transmission of the AE/SAE paper CRF is the preferred method to transmit this information to the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the AE/SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the AE/SAE CRF pages within the designated reporting time frames. • Contacts for AE/SAE reporting can be found in the SRM.

9.4. APPENDIX 4: Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to Nucala by the investigator, will be reported to GSK as described in Section 9.3 (Appendix 3). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating may request continuation of study intervention.

9.5. APPENDIX 5: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

Medical Device Incident Definition
• 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 labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/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
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents

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

Documenting Medical Device Incidents

Medical Device Incident Documenting

- Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Section 9.3 (Appendix 3).
- GSK will ask to investigator about medical device incidents to complete the form.
- 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.

9.6. APPENDIX 6: STUDY-SPECIFIC PHARMACOVIGILANCE PLAN (SPVP)

sPVP Element	Study-Specific Pharmacovigilance Plan (sPVP) (tick applicable statements)
Supplier/ Vendor PV training	☐ N/A – No supplier/vendor involved that could be in receipt of serious and/or non-serious AEs, pregnancy exposures, and/or incidents related to any GSK product
	☒ Supplier/vendor PV training will be conducted using the agreed method and current, approved content, prior to beginning the study. Training will be completed annually and documented.
Investigator and site staff PV training	☐ N/A – No Investigator and/or site staff involved that could be in receipt of serious and/or non-serious AEs, pregnancy exposures, and/or incidents related to any GSK product
	☒ Investigator and/or site staff PV training will be conducted using the agreed method and current, approved content, prior to beginning the study. Training will be completed annually and documented.
Safety-specific roles	☐ SAP is responsible for identifying, collecting, reporting and reconciling AEs, pregnancy exposures, and/or incidents related to any GSK product
	☒ Investigator/monitoring staff is responsible for identifying, collecting, reporting and reconciling AEs, pregnancy exposures, and/or medical device incidents related to any GSK product
AEs, pregnancy exposures, and incidents collection and reporting processes	The following will be identified, collected, and reported to GSK Japan safety: • serious and/or non-serious AEs, **related** to any GSK product • pregnancy exposures to any GSK product (note: in the case of a pregnancy registry, the registry will manage exposures) • incidents related to any GSK product
	For studies that evaluate a GSK product, consult with SMG Pharma Safety SERM to determine if additional data is required and complete the information below: ☐ Study does not evaluate a GSK product - No additional study-specific safety data is to be collected ☒ Study evaluates a GSK product - No additional study-specific safety data is to be collected ☐ Study evaluates a GSK product - additional study-specific safety data is to be collected
AE, pregnancy exposure, and	☐ GSK Global Adverse Event, Pregnancy Exposure, and Incident Reporting Form for Epidemiology and Health Outcome studies

sPVP Element	Study-Specific Pharmacovigilance Plan (sPVP) (tick applicable statements)
incident collection forms	☒ Alternative collection form(s) will be utilized Investigators will report using the following forms: Adverse Event Report form (Japanese) Pregnancy Initial Notification Form (Japanese) Pregnancy Outcome Form (Japanese) Monitoring staff will report using the following forms: Safety Information Notification Form for CRAs (Japanese) Incident Information Notification Form (Japanese)
Frequency of data review	☒ N/A – No batch reviewing of the data.
	☐ Batch review will be conducted
Reporting process and timelines for AEs, pregnancy exposures and medical device incidents	Severe adverse events, pregnancy exposures, and/or incidents related to any GSK product will be reported to SMG Pharma Safety within 24 hours of awareness of the event. Adverse events will be reported to SMG Pharma Safety within 5 work days of awareness of the event.
Interim study reports	☒ N/A – No interim study reports are planned.
	☐ Interim study reports will be shared with the SERM product specialist / physician for review of the interim report safety data
Reconciliation process	☐ A log of all AEs, pregnancy exposures, and incidents identified during the research will be provided to GSK central safety (for multiple country studies) or local safety (for single country studies) on a Reconciliation Form. Central or local safety will confirm all reports listed on the log are included on the GSK Safety Database.
Study-specific PVP monitoring process	☒ SAP will review the sPVP elements and discuss during regular study team and/or supplier meetings to ensure the plan is working effectively.
	☐ Other, please describe.
Provision of final study report	☐ A summary of AEs, pregnancy exposures, and/or incidents related to any GSK product will be included in the final study report. The final draft study report will be provided to the SERM product specialist / physician for review and approval where a specific asset is involved.