Statistical Analysis Plan

Study ID: 213684

Official Title of Study: A single arm, multi-center study to assess the long-term realworld safety and effectiveness of Nucala in EGPA patients who have already used Nucala for at least 96 weeks in Japan

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TITLE PAGE

Protocol 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
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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1.0	8 Apr 2022	Amendment 01	Not Applicable	Original version
2.0	15 Jun 2022	Amendment 01	Section 4.3.1.2: Added calculation of annualized rate for retrospective period. Clarified definition of total duration of OCS administration. Added derivation method of eosinophil count. Section 6.2.2 or Section6.2.4: Corrected the ambiguous wording of "first dose of Nucala". Section 6.2.2: Added the definition of observation period for missing case.	Clarifications and additional considerations were required for valid analyses.
3.0	12 Dec 2022	Amendment 01	Added summaries for: - ANCA+/- - EGPA remission - Immuno-suppressive therapy - Asthma exacerbation - Average daily dose of OCS - Annualized rate of hospitalization for EGPA-related events - Annualized rate of ER/unscheduled visit for EGPA-related events	Clarifications and additional considerations were required for valid analyses.
4.0	18 Apr 2023	Amendment 01	"Active + worsening" category was added for the summaries of clinical	Clarifications and additional considerations

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			symptoms as assessed by 9 organ-systems Analysis of Annualized Rate (event/year) of Asthma Exacerbation for each of the 3 categories is added The definition of follow-up is changed The definition and the assessment point of EGPA relapse is changed A line plot is added for OCS	were required for valid analyses.
5.0	17 May 2023	Amendment 01	The duration between the start of retrospective period to the end of observation period summary were added The definition of the observation period and the follow-up period is changed	They are considered imperative to evaluate the safety of Nucala. The definition is aligned with the standard exposure definition of Mepolizumab.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study 213684.

This SAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

If a post-hoc analysis is required after the planned analysis has been performed, a separate analysis specification will be prepared for that purpose.

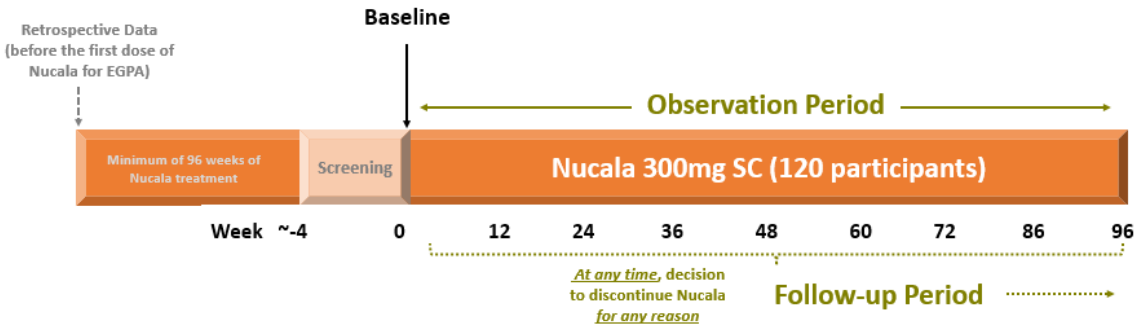
1.1. Objectives and Endpoints

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 • Proportion of participants in the dosing categories[*] relative to average

Objectives	Endpoints
	daily OCS (prednisolone-equivalent) over 96 weeks * 0 mg/day, 0 mg/day < ≤ 4.0 mg/day, 4.0 mg/day < ≤ 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.
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.

1.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	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.
Study interventio n	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 the protocol 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 the protocol 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.
Study intervention Assignment	Not Applicable
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 does not lead to a decision to amend the design or to stop the study. The interim analysis is carried out using interim dataset. All required database cleaning activities in accordance with the Data Management Plan (DMP) have been completed and interim database lock (DBL) has been declared by Data Management.

	Also, the interim analysis is performed for presentation at academic conference using dataset including data until 48 weeks post-exposure.. The Clinical Study Report is created at the interim analyses.
Final Analysis	The final planned analyses will be performed after the completion of the following sequential steps: 1. All participants have completed the study or been withdrawn as defined in the protocol. 2. All required database cleaning activities have been completed and final DBL has been declared by Data Management. The Clinical Study Report will be created at the final analyses.

2. STATISTICAL HYPOTHESES

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.

3. ANALYSIS SETS

The populations for analyses are defined as below.

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened Population	• All participants who signed the ICF and who completed the screening.	• Study Population • Screening Failure
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 Population who have received at least 1 injection of Nucala.	• Study Population • Safety • Efficacy

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The study population analyses will be based on the All Subjects Enrolled (ASE) population, unless otherwise specified. The Treated Population (TP) will be used for all safety and efficacy analyses.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

4.1.2. Baseline Definition

For all endpoints (except for noted in baseline definitions) the baseline values will be derived as below.

If there is unscheduled data on the day of Week 0, the value immediately before Nucala administration will be adopted.

When to be collected		Baseline value
At Screening	At Week 0	
x	-	Screening data
-	x	Week 0 data
x	x	Week 0 data

Retrospective data
Definition
1) Observed data within 12 weeks before the first dose of Nucala for EGPA (i.e. (date of first dose of Nucala – 84 (days) ≤ < date of first dose of Nucala) • Clinical symptoms as assessed by 9 organ-systems • Concomitant medication • Medical/Surgical procedures • Clinical laboratory parameters • Lung function • Ejection fraction 2) Observed data within 48 weeks before the first dose of Nucala for EGPA (i.e. (date of first dose of Nucala – 336 (days) ≤ < date of first dose of Nucala) • Hospitalization for EGPA-related events • ER/Unscheduled visit for EGPA-related events • Asthma exacerbations The retrospective data will be summarized in the same manner as the observation period.

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of endpoint(s)

The primary endpoints are as follows:

- 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)

4.2.2. Main analytical approach

The primary analyses will be based on the TP. Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), with the maximum intensity of each AE determined by the investigator (as mild, moderate, severe or unknown).

All AEs, ADRs, SAEs, AEs leading to withdrawal from study, and AESIs will be summarized by the observation period and the total period (the observation period and the follow-up period), respectively. A separate summary of AEs by maximum intensity will be produced by the observation period and the total period, respectively.

The frequency and percentage of all AEs will be summarized and displayed in two ways: 1) in descending order by PT only and 2) in descending order by SOC and PT.

Separate summaries will be provided for ADRs. An ADR is defined as an AE for which the investigator classifies the possible relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as 'Yes' or missing. The summary table will be displayed by SOC and PT. The relationship of primary SOCs, Preferred Terms, and verbatim texts will be listed.

The number and percentage of participants who experienced the serious adverse event will be summarized.

The following will be considered adverse events of special interest (AESI) for the purpose of analyses: Hypersensitivity (including anaphylaxis), infections and malignant tumors, defined as safety specifications in the Japanese RMP.

AESI	Definition	Dictionary code
Hypersensitivity (including anaphylaxis)	Anaphylaxis reaction (SMQ/narrow)	20000021 (narrow)
	Excluding "10078117: Eosinophilic granulomatosis with polyangiitis" from PT contained in Hypersensitivity (SMQ/narrow)	20000214 (narrow)
Infections	Infections: Infections and infestations(MedDRA/J SOC)	MedDRA/J SOC: 10021881
Malignant tumors	Malignant tumors (SMQ/narrow)	20000227 (narrow) 20000228 (narrow)
	Lymphoma malignum (SMQ/narrow)	20000215 (narrow)

The summary be provided for AESI. The percentage will be calculated in two ways; one with number of participants with event as the denominator and the other with total number of participants as the denominator. The worst-case approach will be applied at participant level for the maximum intensity (i.e. a participant will only be counted once as the worst case from all the events experienced by the participant). For action taken to an event, a participant will be counted once under each action (e.g. if a participant has an event leading to both study discontinuation and dose reduction, the participants will be counted once under both actions).

Listings of all AEs and of subject numbers for individual AEs will be displayed. Reasons for considering as a SAE, AEs leading to withdrawal from study and AESIs will also be listed. In addition, patient profiles will be provided of patients with deaths.

Exposure-adjusted AE rate (the number of events per 1000 participant-years of exposure) for the AEs will also be summarized. This summary table will be produced by the

observation period and the total period (the observation period and the follow-up period), respectively.

The number of events per 1000 participant-years of exposure will be calculated as:

(1000 × number of AEs during the period) / (total duration of exposure in days / 365.25)

The derivation of the total duration of exposure in days is defined in 6.2.3.

4.2.3. Sensitivity analyses

Not Applicable

4.3. Secondary Endpoint(s) Analyses

4.3.1. Secondary endpoint(s)

4.3.1.1. Definition of endpoint(s)

The secondary endpoints are as follows:

- 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
- 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 the observation period
- The proportion of participants in the dosing categories* relative to average daily OCS (prednisolone-equivalent) over the observation period
  * 0 mg/day, 0 mg/day < ≤ 4.0 mg/day, 4.0 mg/day < ≤ 7.5 mg/day, 7.5 mg/day <

4.3.1.2. Main analytical approach

The secondary analyses will be based on the TP. All endpoints will be summarized by using appropriate descriptive statistics.

4.3.1.2.1. Clinical Symptoms as Assessed by 9 Organ-systems

Endpoint
Proportion of participants with clinical symptoms as assessed by 9 organ-systems
Specification

The frequency and percentage of participants with clinical symptoms as assessed by each of 9 organ-systems will be summarized for each assessment time point (Retrospective period and Week 0: “none”, “active”, Week 12 and after: “none”, “active”, “worsening”, “active + worsening”). The frequency and percentage of participants without clinical symptoms as assessed by 9 organ-systems will be summarized for each assessment point. Patients with at least one "worsening" at each assessment point will also be summarized. In addition, line plots will be produced by 9 organ-systems. They will be displayed for the observation period and by the follow-up period separately.

4.3.1.2.2. EGPA Relapse

Endpoint
Proportion of participants with EGPA relapse
Specification
The frequency and percentage of participants with EGPA relapse for the observation period and for the follow-up period will be summarized. The frequency and percentage of participants with EGPA relapse will be categorized as 1 time, 2 times, and ≥3times, and summarized. The frequency and percentage of EGPA relapse and the events that cause EGPA relapse (1-3 in the Step1 below) will also be summarized. A separate summary will be displayed for the events that cause EGPA relapse. A listing of EGPA relapse will also be produced. **Determination of EGPA relapse** EGPA relapse is defined as any of the following events 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 clinical symptoms as assessed by 9 organ-systems. ** Immuno-suppressive agents: If the dose of immuno-suppressive agents increases for the same formulation or if the number of immuno-suppressive agents increases for EGPA treatment. Event date is defined as: 1) Increased dose of OCS: **Date of increased dose** 2) Initiation/increased dose of immuno-suppressive agents: **Date of initiation/Date of increased dose** 3) EGPA treatment with hospitalization: **Date of hospitalization** The first relapse occurred between two consecutive assessment time points will be counted as EGPA relapse for the first of the two assessment points. When assessment time points are scattered (i.e. Week 24 data is missing due to no clinic visit), events

occurred within the last visit date + 84 days will be used as the determination for EGPA relapse.

Definition of Relapse Date

Set the starting point date for each of the following relapse conditions 1) to 3) and calculate the time to relapse (day).

The formula for calculating the time to relapse is relapse date – starting point date + 1

However, if the conditions 1) to 3) overlap, the shortest time (day) until relapse will be used.

1) Increase in OCS dose

- The date of relapse is the date of dose increase.
- The starting point date is the date of the end of dosing immediately before the dose increase or the earliest assessment date without symptoms of EGPA and dose reduction.

ex1) In the case of [dose reduction → discontinuation → dose increase], the starting point date is the end date of dosing (if the end date of dosing is missing, the start date of dosing) immediately before the most recent discontinuation before relapse date.

Assessment time points	Assessment date	EGPA symptoms	Start or end date of dosing	Condition of dosing	Dose (mg)
Nucala start date	2020/1/1	None		Ongoing since before Nucala dosing	10
			2020/1/2	End date of dosing	10
			2020/1/3	Start date of dosing	5
Week 12	2020/4/15			Ongoing dosing	5
			2020/4/16 (Starting point date)	End date of dosing	5
Week 24	2020/7/2	**Active**			None
			2020/7/3 (Relapse date)	Start date of dosing	**10 (Increase)**

ex2) In the case of [dose reduction → dose increase], the starting point date is the start date of dose reduction immediately before relapse date.

Assessment time points	Assessment date	EGPA symptoms	Start or end date of dosing	Condition of dosing	Dose (mg)
Nucala start date	2020/1/1	None		Ongoing since before Nucala	10

				dosing	
			2020/1/2	End date of dosing	10
			2020/1/3 (Starting point date)	Start date of dosing	5
Week 12	2020/4/15	None		Ongoing dosing	5
				Ongoing dosing	5
Week 24	2020/7/2	**Active**	2020/7/2	End date of dosing	5
			2020/7/3 (Relapse date)	Start date of dosing	**10 (Increase)**

ex3) In the case of no dose reduction after Nucala dosing, the starting point date is the earliest assessment date without symptoms of EGPA.

Assessment time points	Assessment date	EGPA symptoms	Start or end date of dosing	Condition of dosing	Dose (mg)
Nucala start date	**2020/1/1 (Starting point date)**	None		Ongoing since before Nucala dosing	5
				Ongoing dosing	5
Week 12	2020/4/15	None		Ongoing dosing	5
			2020/4/16	End date of dosing	5
Week 24	2020/7/2	**Active**			None
			2020/7/3 (Relapse date)	Start date of dosing	**10 (Increase)**

2) Increasing the dose or initiation of immune-suppressive agents.

- Dose increases will be treated in the same way as for OCS.
- The date of relapse associated with new initiation is the start date of dosing.
- The starting point date is the earliest assessment date without symptoms of EGPA.

ex) The starting date is the earliest assessment date without symptoms of EGPA.

Assessment time points	Assessment date	EGPA symptoms	Start or end date of dosing	Condition of dosing	Dose (mg)
Nucala start date	2020/1/1	**Active or worsening**			None
					None
Week 12	**2020/4/15 (Starting point date)**	None			None

					None
Week 24	2020/7/2	**Active or worsening**			None
			2020/7/3 (Relapse date)	Start date of dosing	**10 (New initiation)**

3) Treatment involving hospitalization

- The date of relapse is the date of hospitalization.
- The starting point date is the date of discharge immediately prior to relapse or the earliest assessment date without symptoms of EGPA.

ex1) If there is a discharge date immediately before the relapse, the starting point date is the discharge date immediately before the relapse.

Assessment time points	Assessment date	EGPA symptoms	Date of hospitalization or discharge	Condition of hospitalization or discharge
Nucala start date	2020/1/1	**Active or worsening**		Ongoing hospitalization
			2020/1/2 (Starting point date)	Date of discharge
Week 12	2020/4/15	None		
			2020/6/13 (Relapse date)	**Date of hospitalization**
Week 24	2020/7/2	**Active or worsening**		Ongoing hospitalization

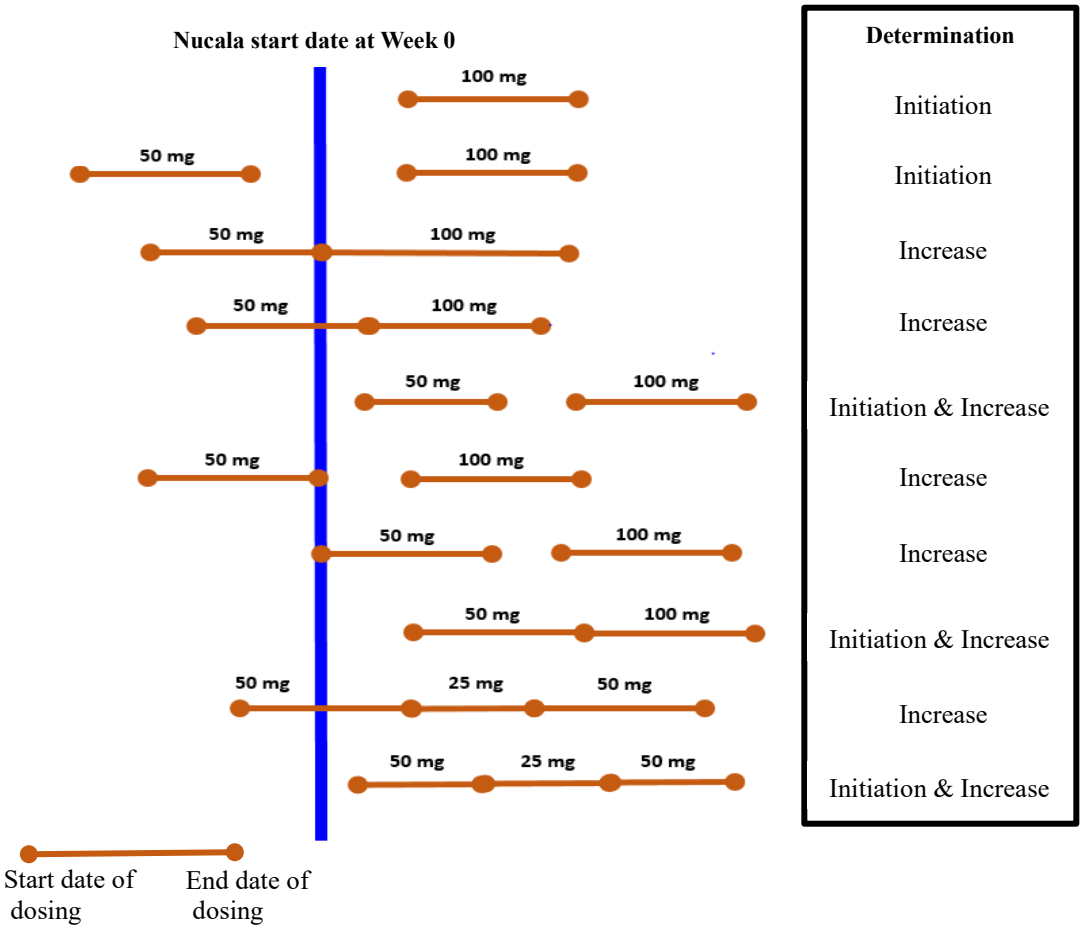
ex2) If there is no discharge date immediately prior to relapse or if there is no discharge date exists (e.g. ongoing hospitalization, incomplete date), the starting point date is the earliest assessment date without symptoms of EGPA.

Assessment time points	Assessment date	EGPA symptoms	Date of hospitalization or discharge	Condition of hospitalization or discharge
Nucala start date	2020/1/1	**Active or worsening**		
Week 12	**2020/4/15 (Starting point date)**	None		
			2020/6/13 (Relapse date)	**Date of hospitalization**
Week 24	2020/7/2	**Active or worsening**		Ongoing hospitalization

Increased dose of OCS & Initiation/increased dose of immuno-suppressive agents

The decision to increase the dose of OCS and to Initiation or increased dose of immuno-suppressive agents will be made as follows.

	Condition
Increased dose	The day after the visit date of Week 0 in this study: OCS: In case of the dose of OCS increased as prednisolone-equivalent Immuno-suppressive agents: In case of the dose of immune-suppressive agents increased for the same formulation or if the number of immune-suppressive agent increased
Initiation	In case of an immune-suppressive agent is newly started (or the number of agents is added) after the start date of Nucala. However, this does not apply if the same agent is re-administered after the start of administration of the agent.



4.3.1.2.3. Annualized Rate of Hospitalization for EGPA-related Events

Endpoint
Annualized rate (event/year) of hospitalization for EGPA-related events

Model Specification

The annualized rate of hospitalization for EGPA-related events will be analyzed by using a negative binomial generalized linear model with logarithm of time as an offset variable, without covariate. The annualized rate and associated 95% CIs will be calculated by exponential transform the value of intercept term and associated 95% CIs estimated when the above model was applied. The annualized rate will be calculated in observation period and retrospective period independently.

Terms in the model:

- **Response**: number of recorded, on-treatment, hospitalization for EGPA-related events experienced per participant.
- **Offset**: logarithm of treatment time in year

  Observation period:

  Treatment time in year for each participant will be calculated as:

  Participants who complete the study:

  {(date of end of Nucala – date of start of Nucala) + 1} / 365.25

  Participants who enter the follow-up period:

  {(date of end of Nucala + 28 – date of start of Nucala) + 1} / 365.25

  For the raw value of calculation result, round off to two decimal places will be applied.

  If the date of end of Nucala is missing, the date of start of the last administration of Nucala + 28 days will be imputed for the date of end of Nucala.

  Retrospective period:

  Treatment time in year for each participant will be calculated as:

  48 / 52

SAS code:

```
proc genmod data = <dataset>;
  model n_hosp =
/ link=log dist=negbin offset=logfuinyears;
run;


data parm_est(keep= val rate rate_ll rate_ul);
  set out_parm(where=(parameter='Intercept'));
  format rate rate_ll rate_ul 8.2;
  val= "annualized rate of hospitalization for EGPA-related events
from negative binomial model without covariate";
  rate=exp(estimate);
  rate_ll=exp(lowerwaldcl);
  rate_ul=exp(upperwaldcl);
run;
```

where n_hosp is the number of hospitalizations for EGPA-related events per participant in follow-up time, and logfuinyears is logarithm of the treatment time in years.

4.3.1.2.4. Annualized Rate of Emergency Room/Unscheduled Visit for EGPA-related Events

Endpoint
Annualized rate (event/year) of emergency room/unscheduled visit for EGPA-related events
Model Specification
The annualized rate of emergency room/unscheduled visit for EGPA-related events will be analyzed by using a negative binomial generalized linear model with logarithm of time as an offset variable, without covariate. The annualized rate and associated 95% CIs will be calculated by exponential transform the value of intercept term and associated 95% CIs estimated when the above model was applied. The annualized rate will be calculated in observation period and retrospective period independently. Terms in the model: • **Response**: number of recorded, on-treatment, emergency room/unscheduled visit for EGPA-related events experienced per participant. • **Offset**: logarithm of treatment time in year *Observation period:* Treatment time in year for each participant will be calculated as: Participants who complete the study: {(date of end of Nucala – date of start of Nucala) + 1} / 365.25 Participants who enter follow-up period: {(date of end of Nucala + 28 – date of start of Nucala) + 1} / 365.25 For the raw value of calculation result, round off to two decimal places will be applied. If the date of end of Nucala is missing, the date of start of the last administration of Nucala + 28 days will be imputed for the date of end of Nucala. *Retrospective period:* Treatment time in year for each participant will be calculated as: 48 / 52 SAS code: `proc genmod data = <dataset>;`

```
  model n_emv =
/ link=log dist=negbin offset=logfuinyears;
run;


data parm_est(keep= val rate rate_ll rate_ul);
  set out_parm(where=(parameter='Intercept'));
  format rate rate_ll rate_ul 8.2;
  val= "annualized rate of emergency room/unscheduled visit for
EGPA-related events from negative binomial model without
covariate";
  rate=exp(estimate);
  rate_ll=exp(lowerwaldcl);
  rate_ul=exp(upperwaldcl);
run;
```

where n_emv is the number of emergency room/unscheduled visit for EGPA-related events per participant in follow-up time, and logfuinyears is logarithm of the treatment time in years.

4.3.1.2.5. Average daily dose of OCS and Dosing categories

Endpoints

- Average daily dose (prednisolone-equivalent) of OCS
- The proportion of participants in the dosing categories relative to average daily OCS (prednisolone-equivalent)

Specification

To calculate the dose of OCS by prednisolone equivalent, multiply by the following coefficients.

Generic name	GSK Drug Code	Prednisolone equivalent value	Coefficient
Hydrocortisone	00028601	20	0.250
Hydrocortisone succinate	00028602	20	0.250
Cortisone acetate	00014602	25	0.200
Prednisolone	00016201	5	1.000
Prednisolone succinate	00016203	5	1.000
Methylprednisolone	00049601	4	1.250
Methylprednisolone succinate	00049602	4	1.250
Triamcinolone	00031901	4	1.250
Triamcinolone acetonide	00031902	4	1.250
Dexamethasone	00016001	0.75	6.667
Dexamethasone phosphate	00016002	0.75	6.667
Paramethasone acetate	00066402	2	2.500
Betamethasone	00008501	0.75	6.667
Betamethasone phosphate	00008502	0.75	6.667

Average daily dose of OCS for each participant will be calculated by 12-weekly periods and the retrospective period as:

Total dosage of OCS (mg) / Total duration of administration of OCS (day)

Total duration of administration is defined as:

- By 12-weekly period

  Last date of each period – later date of (first date of each period or start date of OCS) +1

  12-weekly period is described in Section 6.2.4. If OCS is administered and then OCS is no longer required on the last date of each period, 0 mg will be imputed.

- Retrospective period

  Last date of retrospective period– later date of (start date of retrospective period or start date of OCS) + 1

  Average daily OCS in the retrospective period will be calculated if a participant uses OCS in the retrospective period, otherwise average daily OCS will be 0 mg. If OCS is administered and then OCS is no longer required on the last date of the retrospective period, 0 mg will be imputed.

Over observation period

Last day of observation period (Week 48 for interim analysis, if participant is on-going on observation period) - later date of (date of dose of Nucala at Week 0 or start date of OCS) +1.

If the date of dose of Nucala at Week 0 is missing, the latest available date between the date of screening visit and the date of visit at week 0 will be used for calculation of observation period. If OCS is administered and then OCS is no longer required during the observation period, 0 mg will be imputed.

When more than one OCS is administered to a participant in the same period, the sum of OCS doses will be used as daily OCS dose.

Summary statistics of average daily dose of OCS will be calculated by the retrospective period and 12-weekly periods. Average daily dose of OCS percent change from Week 0 and from retrospective period will also be summarized by 12-weekly periods. A box plot and a line plot of the median average daily dose of OCS will be produced.

Average daily dose of OCS percent change from Week 0 and from retrospective period is calculated as:

Percent change = ((average daily dose of OCS at each 12-weely period - average daily dose of OCS at Week 0 (or retrospective period))/ average daily dose of OCS at Week 0 (or retrospective period))*100 (%)

The frequency and percentage of participants in the following dosing categories relative to average daily OCS will be summarized by the retrospective period and 12-weekly periods. The denominator of the frequency is the TP. A line plot of the percentage of patients with 0 mg/day of average daily OCS will be presented.

Daily OCS dosing category:

- 0 mg/day, 0 mg/day < ≤ 4.0 mg/day, 4.0 mg/day < ≤ 7.5 mg/day, 7.5 mg/day <
- 0 mg/day < ≤ 2.0 mg/day, 2.0 mg/day < ≤ 4.0 mg/day

4.3.1.3. Sensitivity analyses

Not Applicable

4.4. Exploratory Endpoint(s) Analyses

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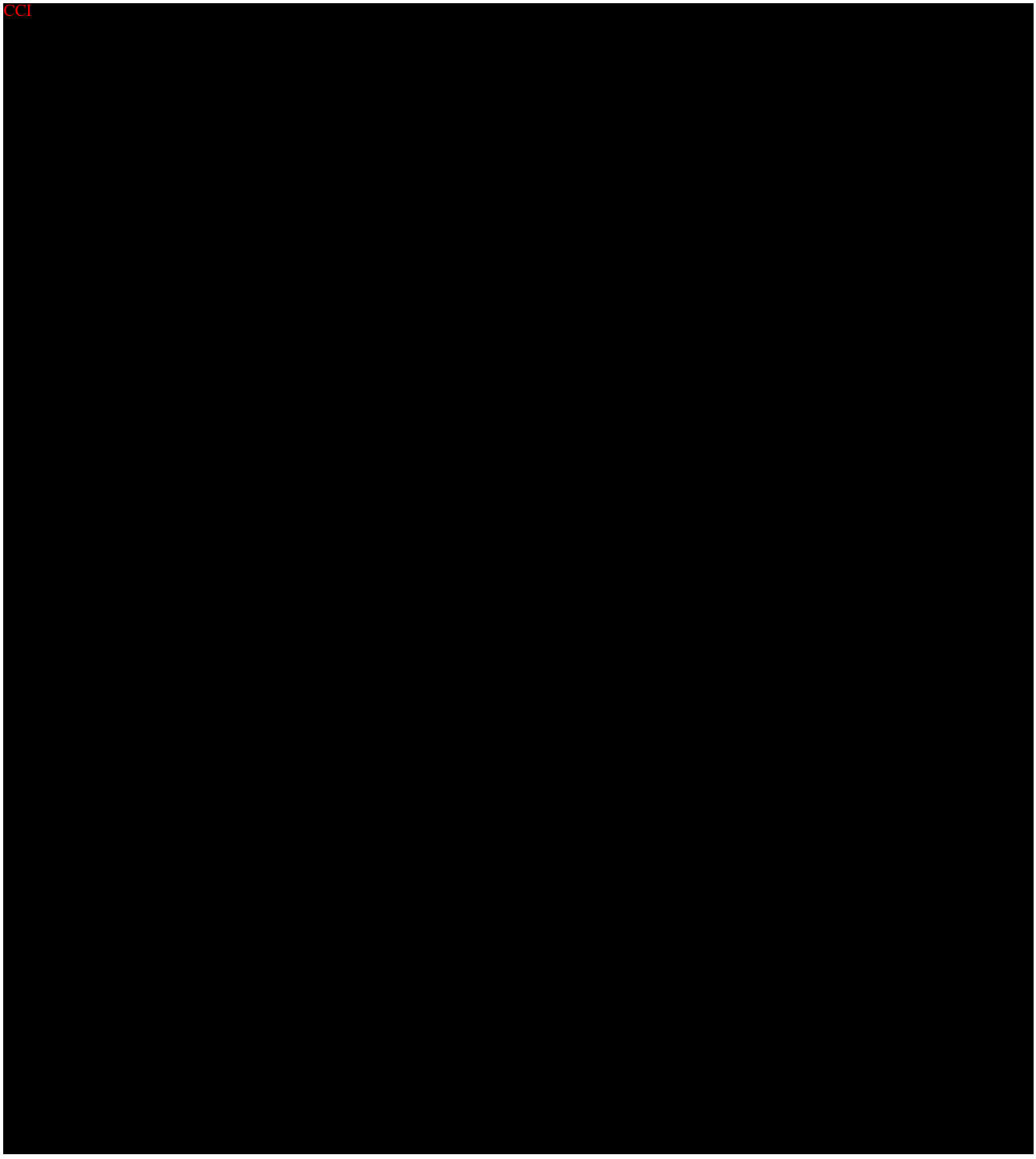

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[redacted]

4.5. Other Safety Analyses

4.5.1. Extent of Exposure

The frequency and percentage of exposure to Nucala will be summarized for each of the following categories by the observation period and the follow up period, based on the TP. The extent of exposure will also be listed.

- Nucala 300mg SC only
- Other than the above (e.g., dose reduction of Nucala)

The duration in days between the first dose of Nucala for EGPA in the retrospective period and the last dose of Nucala in the observation period will be summarized.

4.5.2. Adverse Events

Refer to the primary endpoint analyses.

4.5.2.1. COVID-19 Assessment and COVID-19 AEs

AEs of all participants with COVID-19 will be listed for the TP.

4.5.2.2. Impact of COVID-19 Pandemic on Safety Results

Not Applicable

4.6. Other Analyses

4.6.1. Profile plot

A participant profile plot including the following items will be created.

- OCS daily dose
- No clinical symptoms as assessed by 9 organ-systems at all
- EGPA relapse
- An increased dose or addition of immuno-suppressive therapy
- Hospitalization related to EGPA worsening

4.6.2. Immuno-suppressive Therapy

The frequency and percentage of participants with no immuno-suppressive therapy will be summarized by the retrospective period and12-weekly periods. 12-weekly period is described in Section 6.2.4. A line plot of the percentage of patients with no immuno-suppressive therapy will be presented.

4.6.3. EGPA Remission

EGPA remission is defined as each of the combinations of the clinical symptoms as assessed by 9 organ-systems and average daily dose of OCS.

- Participants with no clinical symptoms as assessed by 9 organ-systems
- Participants with no "worsening" clinical symptoms as assessed by 9 organ-systems
- Participants with average daily dose of OCS in ≤ 4.0 mg/day

- Participants with average daily dose of OCS in 0 mg/day

The frequency and percentage of participants in EGPA remission by EGPA remission period will be summarized. Line plots by EGPA remission period will also be produced for the proportion of participants with average daily dose of OCS in ≤ 4.0 mg/day and in 0 mg/day. The plots will be displayed for the participants with no clinical symptoms as assessed by 9 organ-systems and no "worsening" clinical symptoms separately.

The period for EGPA remission is defined as follows:

EGPA remission period	**Clinical symptoms as assessed by 9 organ-systems**	**Average daily dose of OCS**
Week 12/Weeks 9-12	Week 12	Weeks 9-12
Week 24/Weeks 21-24	Week 24	Weeks 21-24
Week 36/Weeks 33-36	Week 36	Weeks 33-36
Week 48/Weeks 45-48	Week 48	Weeks 45-48
Week 60/Weeks 57-60	Week 60	Weeks 57-60
Week 72/Weeks 69-72	Week 72	Weeks 69-72
Week 84/Weeks 81-84	Week 84	Weeks 81-84
Week 96/Weeks 93-96	Week 96	Weeks 93-96

4.6.4. Subgroup analyses

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:

- Period from EGPA diagnosis to Nucala administration (year) (≤ 1, 1 < ≤ 2, 2 < ≤ 5, 5 < ≤ 10, 10 <)
- Severity of EGPA disease (1-2, 3, 4-5)
- Average daily dose (prednisolone-equivalent) of oral corticosteroid (OCS) over the observation period (0 mg/day, 0 < ≤ 4 mg/day, 4 < ≤ 7.5 mg/day, 7.5 mg/day <)
- ANCA (Positive, Negative)
- Immuno-suppressive therapy (Yes, No)

- EGPA disease relapse (Yes, No)

The following will be presented for each subgroup, based on the TP:

- summary of all AEs by the observation period and by the total period (the observation period and the follow-up period)
- frequency of participants with clinical symptom assessed by 9 organ-systems at each assessment visit by the observation period
- frequency of participants with EGPA relapse by the observation period
- summary of average daily dose of OCS at each assessment visit by the observation period
- plot of participants with clinical symptom assessed by 9 organ-systems at each assessment visit by the observation period
- box plot of median of average daily dose of OCS at each assessment visit by the observation period
- line plot of median of average daily dose of OCS at each assessment visit by the observation period In addition, the demographic and baseline characteristics will be summarized for the following subgroups.
- Completion/Discontinuation of the study
- With/Without clinical symptoms as assessed by 9 organ-systems at Week 48 and Week 96

Subgroup	EP1	EP2	EP3	EP4
Period from EGPA diagnosis to Nucala administration	Y	Y	Y	Y
Severity of EGPA disease	Y	Y	Y	Y
Average daily dose (prednisolone-equivalent) of oral corticosteroid (OCS) over the observation period	Y	Y	-	Y
ANCA	Y	Y	Y	Y
Immuno-suppressive therapy	Y	Y	Y	Y
EGPA disease relapse	Y	-	Y	Y

EP1: Proportion of participants with each of the clinical symptoms as assessed by 9 organ-systems
EP2: Proportion of participants with EGPA relapse
EP3: Average daily dose (prednisolone-equivalent) of oral corticosteroid (OCS) over the observation period
EP4: Frequency of Adverse events (AEs)

The above categories may be reconsidered a more appropriate level, and additional subgroup categories will be planned in the further analysis.

4.7. Interim Analyses

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

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 01 (Dated: 27-JUL-2020).

5. SAMPLE SIZE DETERMINATION

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.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the All Subjects Enrolled (ASE) population or Treated Population (TP), unless otherwise stated.

6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study and screening failure will be provided. Reasons for study withdrawal and screening failure will also be summarized and listed. Those who have discontinued Nucala treatment but not withdrawn from study will be categorized as study completion. Screen failure summary will be based on the screened population.

The number and percentage of participants who completed Nucala treatment as well as the number who discontinued Nucala treatment prior to the end of the study will be summarized, along with the reasons for discontinuation of Nucala treatment, and these will also be listed for the TP population.

The number and percentage of participants who entered in the observation period and in the follow-up period will be summarized. Participants who have discontinued the treatment of Nucala on or after the first treatment discontinuation +29 days are defined as the participants in the follow-up period.

Study completion, early withdrawal and screening failure are defined as follows.

Type	Definitions
Study completion	A participant completed the observation period, which is scheduled for 96 weeks (approximately 2 years) at maximum.
Early withdrawal	A participant who was enrolled to this study but withdrew during the observation period.
Screening failure	A participant who consented to participate in the study but did not meet the eligibility criteria at Screening.

6.1.2. Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized with descriptive statistics and listed based on the TP.

Demographic and baseline characteristics	Detail
Sex	Male Female

Demographic and baseline characteristics	Detail
Age (year)	1) Continuous 2) < 15, 15 ≤ < 65, 65 ≤ < 75, 75 ≤ 3) < 65, 65 ≤
Height (cm)	Continuous
Weight (kg)	1) Continuous 2) ≤ 70, 70 < ≤ 85, 85 <
BMI (kg/m^2) BMI (kg/m^2) = weight (kg) / [height (m)]^2	Continuous
Severity of EGPA disease Defined by Japan Intractable Diseases Information Center (Japan Intractable Diseases Research Foundation)	1, 2, 3, 4, 5
Duration of EGPA disease (year)	1) Continuous 2) ≤ 2, 2 < ≤ 5, 5 < ≤ 10, 10 <
Medical conditions	Yes No
Concomitant medications	Yes No
Clinical symptoms (9 organ-systems) i.e. systemic, skin, mucous membranes/eyes, ears/nose/throat, chest, cardiovascular, abdominal, renal, nervous system	Yes No by 9 organ-systems
Hospitalization for EGPA-related events during the Retrospective period	Yes No
ER/Unscheduled visit for EGPA-related events during the Retrospective period	Yes No
Asthma exacerbation during the Retrospective period	Yes No
Clinical laboratory parameters: haematological parameters test CCI [redacted]	Continuous
	Continuous

6.1.3. Protocol Deviations

No per protocol analysis is planned for this study.

Important protocol deviations will be summarized and listed for the ASE. A listing of subjects with inclusion/exclusion criteria deviations will also be provided.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP), which is specifically developed for this study.

Data will be reviewed prior to DBL (database lock) to ensure all deviations are captured and categorized in the protocol deviations AR dataset.

The deviations dataset will be the basis for these summaries and listings.

The visits impacted by COVID-19 will be summarized and listed for the ASE.

6.1.4. Medical Conditions and Concomitant Medications

Current medical conditions are defined as currently occurring diseases at screening. Past medical conditions are defined as diseases not occurring at screening but in the past. Medical conditions will be summarized by current and past for the ASE.

Concomitant medications (other products, corticosteroid, immunosuppressants, and immunoglobulin) will be coded using the GSK Drug. The summary of concomitant medications will be provided by ingredient (i.e. multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients). The summary will be created using ingredient base names (i.e. ingredients with the same base name but different salt will appear under one base name in the summary). Anatomical Therapeutic Chemical (ATC) classifications will not appear in the summary.

Summaries of concomitant medications will be provided for the observation period, the follow-up period and the retrospective period. Concomitant medications will also be listed by ingredient. They will be displayed for the ASE.

Classification of a concomitant medication into study phase (at study entry, screening/run-in period, stabilization period, on-treatment, post-treatment, or post-study) will be made with reference to the study phase as defined above. A medication will be classified into every period in which it was taken. For medications with partial start and stop dates, the medication will be classified into every period in which it could have been taken.

6.1.5. Medical/Surgical Procedures

The frequency and percentage for each EGPA therapy (i.e., plasma exchange therapy, operation therapy and other therapies) will be summarized by the retrospective period, the observation period and the follow-up period. This will be based on the ASE.

6.1.6. Pregnancy

All pregnancy of participants and their partners during the study will be listed, based on the TP.

6.1.7. Additional Analyses Due to the COVID-19 Pandemic

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF. The number and percentage of participants with a suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be summarized for the TP.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

Not Applicable

6.2.2. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study period.

Screening period is defined as 0-4 weeks before the date of dose of Nucala at Week 0.

Observation period is defined as time from the date of dose of Nucala at Week 0 to the stop date of Nucala +28 days for the participants who did not withdraw from study, or the first treatment discontinuation date +28 days for the participants who withdraw from study . If the date of dose of Nucala at Week 0 is missing, the latest available date between the screening visit date and the Week 0 visit date will be used for the start date of the observation period. When the last Nucala stop date is missing, the last Nucala start date will be imputed.

Follow-up period is defined as time from the first treatment discontinuation date +29 days to 96 weeks within the observation period at maximum. The follow-up period is only applicable for the participants who discontinued the treatment.

Retrospective period is defined as time (within 12 weeks) before the first dose of Nucala. For data of hospitalization for EGPA-related events and ER/Unscheduled visit for EGPA-related events the period is defined as time (within 48 weeks) before the first dose of Nucala.

The study periods to use for summaries on each endpoint are as below.

Participants who completed the study

A: Retrospective period	PMS period	B: Observation period

Participants who discontinued and moved to the follow-up period

C: Retrospective period	PMS period	D: Observation period	E: Follow-up period

6.2.3. Study Day and Nucala Stop Date

The study day will be calculated relative to visit date of Week 0 and as the number of days from Week 0:

- Ref Date = Missing then Study Day = Missing
- Ref Date < Week 0 then Study Day = Ref Date – Week 0
- Ref Date ≥ Week 0 then Study Day = Ref Date – (Week 0) + 1

The duration of exposure to Nucala is calculated as (Nucala stop date – Nucala start date + 29). If overall Nucala stop date is missing, the last Nucala start date will be imputed.

6.2.4. Assessment Window

The assessment time points defined below are used in the analysis. When calculating the assessment date, the visit closest to the specified date is used, and if the period from the specified date is the same, the latest visit is used.

Assessment window will be applied to early withdrawal dates. If participants prematurely withdraw from the study and do not have the visit date of Week 96, 673 days after Week 0 will be imputed to missing visit date of Week 96.

If the derived data based on the study day is included in the range of period, the corresponding week is assigned as below and will be used for analysis.

Assessment time points	Specified date	Window (±day)	Period (day)	
			From	to
Week 0	1	-	-28	1
Week 12	85	28	57	113
Week 24	169	28	141	197
Week 36	253	28	225	281
Week 48	337	28	309	365
Week 60	421	28	393	449
Week 72	505	28	477	533
Week 84	589	28	561	617
Week 96	673	28	645	701

The following shows the assessment window for the follow-up period.

Assessment time point	Specified date	Window (±day)	Period (day)	
			From	to
Follow Week 0	1	-	-	1
Follow Week 12	85	28	57	113
Follow Week 24	169	28	141	197
Follow Week 36	253	28	225	281

Assessment time point	Specified date	Window (±day)	Period (day) From	to
Follow Week 48	337	28	309	365
Follow Week 60	421	28	393	449
Follow Week 72	505	28	477	533
Follow Week 84	589	28	561	617
Follow Week 96	673	28	645	701

OCS dose and immuno-suppressive therapy is recorded on a daily basis and will be averaged into 12-weekly periods as below. If the date of dose of Nucala at Week 0 is missing, the latest available date between the screening visit date and the Week 0 visit date will be used for the start date of the observation period.

12-weekly period	First date	Last date
Weeks 9-12	Nucala start date at Week 0 + 56 days	Nucala start date at Week 0 + 84 days
Weeks 21-24	Nucala start date at Week 0 + 140 days	Nucala start date at Week 0 + 168 days
Weeks 33-36	Nucala start date at Week 0 + 224 days	Nucala start date at Week 0 + 252 days
Weeks 45-48	Nucala start date at Week 0 + 308 days	Nucala start date at Week 0 + 336 days
Weeks 57-60	Nucala start date at Week 0 + 392 days	Nucala start date at Week 0 + 420 days
Weeks 69-72	Nucala start date at Week 0 + 476 days	Nucala start date at Week 0 + 504 days
Weeks 81-84	start date at Week 0 + 560 days	Nucala start date at Week 0 + 588 days
Weeks 93-96	Nucala start date at Week 0 + 644 days	Nucala start date at Week 0 + 672 days

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6.2.6. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • However, where necessary, display programs may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
Adverse Events	• Partial dates for AE recorded in the eCRF will be imputed using the following conventions: Study start date is defined as the date of dose of Nucala at Week 0. Missing start day: If study start date is missing (i.e. participant did not start study), then set start date = 1st of month. Else if study start date is not missing: o If month and year of start date = month and year of study start date, then • If stop date contains a full date and stop date is earlier than study start

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>date, then set start date= 1st of month.
• Else set start date = study start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study start date is missing (i.e. participant did not start study), then set start date = January 1.
Else if study start date is not missing:
o If year of start date = year of study start date, then
• If stop date contains a full date and stop date is earlier than study start date, then set start date = January 1.
• Else set start date = study start date.
Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/ Medical History</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study start date is missing (i.e. participant did not start study), then set start date = 1st of month.
Else if study start date is not missing:
o If month and year of start date = month and year of study start date, then
• If stop date contains a full date and stop date is earlier than study start date, then set start date= 1st of month.
• Else set start date = study start date.
Else set start date = 1st of month.</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail	
	Missing start day and month	If study start date is missing (i.e. participant did not start study), then set start date = January 1. Else if study start date is not missing: o If year of start date = year of study start date, then • If stop date contains a full date and stop date is earlier than study start date, then set start date = January 1. • Else set start date = study start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation
Age	Age will be calculated based on the screening visit date. Birth date will be imputed as follows: o Any participant with a missing day and month will have this imputed as '30th June'. Birth date will be presented in listings as 'YYYY'.	

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SAS

7. REFERENCES

GlaxoSmithKline PMS protocol No. 208505 NUCALA Subcutaneous Injection Special Drug Use Investigation (EGPA, Long-term) ver. 3.0. 30-Jul-2019.

Post–marketing Surveillance of Mepolizumab Use in Patients with Eosinophilic Granulomatosis with Polyangiitis in Japan: Interim Analysis. Therapeutic Research vol. 42 no. 6 2021.