NUCALA Subcutaneous Injection
Special Drug Use Investigation
（EGPA, Long-term）

Protocol

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1. Objectives

The objective of this study is to collect and assess information on the safety and effectiveness of the long-term use of Nucala subcutaneous injection (hereinafter referred to as "Nucala") in daily clinical practice in patients with Eosinophilic Granulomatosis with Polyangiitis (EGPA).

［Conditions for Approval］As the number of EGPA patients who are inadequate responders to existing therapies in Japanese clinical trials is extremely limited, it is required to conduct a drug use investigation (DUI) after the market launch in all patients until the data are accumulated from an adequate number, thereby enabling the early collection of data regarding safety and effectiveness, and taking necessary measures needed for the proper use of the drug, along with getting a grasp of the characteristics of patients receiving Nucala for EGPA.

2. Safety Specification

In this study, the safety specifications are as follows, and the occurrence, etc. will be monitored.

- Hypersensitivity including Anaphylaxis
- Infections
- Malignant Tumors

3. Target Population

All patients* administered Nucala for the treatment of EGPA after its approval of indication will be included in the study. In addition, after the approval, patients who had already received Nucala for EGPA prior to the conclusion of the contract will also be included.

It also covers patients who had been registered to a special drug use investigation, SDUI (Protocol No.204524) for bronchial asthma, but had a change in treatment purpose from bronchial asthma to EGPA during the observation period.

*：Irrespective of whether patients have a history of Nucala treatment for bronchial asthma or not

4. Target Sample Size and Rationale

Target number of patients: 300 patients (as a safety analysis population)

Rationale:

In a phase III international joint study conducted in EGPA patients (mepolizumab group: 68 patients), the incidence of serious infection defined as the important potential risk was 5.88% (4/68 patients). On the assumption that the incidence used as a threshold is 6%, to confirm that the lower bound of the two-sided 95% CI exceeds the 6% threshold when the real risk exists two times or more, 277 patients are required as a safety analysis population. Accordingly, the target number of patients was set at 300 in consideration of the dropouts.

5. Planned Number of Medical Institutions by Department

All medical institutions where Nucala is administered to EGPA patients

6. Study Period

1. Study conduct

Study period: from the approval of EGPA indication to three months after termination of the observation period in patients eligible for case report form (CRF) collection (period of the follow-up investigation, if conducted) or the lifting of approval conditions, whichever comes later

Observation period: The observation period per patient is up to 96 weeks (2 years) from the start of Nucala administration for EGPA at a maximum. If a patient has withdrawn from/terminated administration of Nucala, it will be until the withdrawal/termination. Additionally, to consider the safety and effectiveness of Nucala administration in patients who had withdrawn from/terminated due to "symptom improvement", the 48-week (1-year) follow-up investigation should be conducted as much as possible.

Scheduled enrolment period: from the approval of EGPA indication to the lifting of approval condition

Patients are eligible for CRF collection when starting Nucala administration for EGPA by 31 October, 2019, and CRFs will be collected as required when patients start the administration since 1 November, 2019. Further, patients are eligible for enrolment when starting the administration by the acknowledgment of the report at a committee meeting, where the all-case investigation-related conditions for approval are lifted, and enrolment will continue.

2. Study end

Final analysis completion: July 2025

Final report preparation completion: December 2025

7. Study Methods

1. Requirements for physicians

   For use of Nucala, confirm that physicians meet any of the following requirements;

   1) Experienced in the treatment of EGPA, certified as a specialist and an instructor in every kind of relevant academic societies
   2) Experienced in the treatment of EGPA, certified as a physician and cooperating physician designated for intractable diseases
   3) Sufficiently experienced in the treatment of EGPA, providing the treatment of EGPA in proper cooperation with physicians who correspond to the above-mentioned
   4) Providing the treatment of EGPA under direct supervision of physicians who correspond to 1 and 2

2. Request and contract for the study

   1) The person in charge of this study (medical representative or monitoring outsourcee) will explain the objectives, target population, study items, study methods, etc. and request cooperation to the planned physicians for the study, etc. at the medical institutions where Nucala had been adopted/delivered for the treatment for bronchial asthma but also have plans to administer the drug to EGPA patients.
   2) If cooperation to the study has been obtained, the Written Contract should be concluded with the heads (e.g. directors, etc.) of the medical institutions before the start of the study.

3. Enrolment of target population

   The study will be conducted using an all-case investigation method.

1) The investigator will record the patient information, etc. on the Enrolment Form regarding all patients eligible for enrolment after the conclusion of the contract, and will fax it to the Enrolment Centre immediately after the start of administration. The personally identifiable information, such as the name, address, date of birth, initials of patients, should not be recorded in the Enrolment Form.

<Enrolment Centre>

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2) After the approval of EGPA indication, the Written Contract should be concluded before the start of administration in principle, however, patients to whom Nucala has unavoidably been administered before the conclusion of the contract will also be enrolled as a retrospective patient.

4. Data collection and case report form (CRF) completion
   1) The investigator will confirm the study items, such as the characteristics of patients eligible for CRF collection.
   2) During the observation period, the investigator will monitor the information about safety and effectiveness, etc.
   3) At the end of the observation period of patients eligible for CRF collection (or at withdrawal/termination, if a patient has withdrawn from/terminated administration of Nucala), the investigator will record the obtained information on the CRF and submit the completed CRF to the person in charge of this study . The personally identifiable information, such as the name, address, date of birth, initials of patients, should not be recorded in the CRF.
5. Confirmation of all-case investigation implementation
   Annually and after the end of the study period, the investigator will confirm whether or not enrolled patients are all receiving Nucala, affix his/her signature or name/seal to the "Confirmation Letter of All-Case Investigation" and submit it to the person in charge of this study.
6. Obtaining Informed Consent
   The investigator will provide a patient eligible for CRF collection (and/or, his/her substitute) with a full explanation on the publication of the study results either verbally, or in writing using an informed consent form and obtain informed consent.

8. Study Items

The investigator will collect the information about the following items, etc. as far as possible and record it on the CRF.

1. Information on medical institution
   Name of a medical institution, department, investigator
2. Patient characteristics (at the start of Nucala administration for EGPA (hereinafter referred to as "at the start of Nucala administration"))
   Identification number, gender, year of birth or age at the start of Nucala administration, start date of Nucala administration, presence and absence of obtained informed consent regarding study result publication, body weight, reasons for use of Nucala, date (month, year) of EGPA diagnosis, severity classification of EGPA[*1] at the start of Nucala administration, presence or absence of hospitalization due to EGPA in 48 weeks before the start of Nucala administration and number of times patient experienced hospitalization, presence and absence of past

medical history/comorbidity (bronchial asthma, renal impairment, hepatic function abnormal, others) and name of disease, presence or absence of history of Nucala use for bronchial asthma if a patient has comorbid bronchial asthma.
To protect the confidentiality regarding identification of an individual patient, the identification number should be a unique number assigned to an individual patient by the investigator, etc.
In this study, any disease, symptom, and allergy history other than EGPA which is present before the start of administration of Nucala but has recovered/resolved by the start of Nucala administration will be handled as a "past history". Meanwhile, any disease, symptom, and allergy other than EGPA which is present at the start of Nucala administration will be handled as a "comorbidity".

[*1] : Severity Classification of EGPA defined by Japan Intractable Diseases Information Center (Japan Intractable Diseases Research Foundation)

3. Administration status of Nucala
   Single dose during the observation period (mg/dose), daily dose frequency (X times per day), administration date, reasons for revision of dosage and administration
4. Pre-treatment medications (during 4 weeks before the start of Nucala administration) and concomitant medications (adrenal cortical steroid (including medications for bronchial asthma), immune-suppressive agent and immunoglobulin preparations only)
   Presence or absence of adrenal cortical steroid (including medications for bronchial asthma), immune-suppressive agent and immunoglobulin preparations during 4 weeks before the start of Nucala administration and during the observation period, name of drugs, daily dose, start date of administration, end date of administration, reasons for administration
5. Concomitant medications (other than adrenal cortical steroid, immune-suppressive agent and immunoglobulin preparations)
   Presence or absence of concomitant medications other than adrenal cortical steroid (including medications for bronchial asthma), immune-suppressive agent and immunoglobulin preparations) during the observation period, name of medications, reasons for use
6. Pre-treatment for EGPA
   Presence or absence of pre-treatment for EGPA before the start of administration, name of treatment
7. Concomitant therapies for EGPA
   Presence or absence of concomitant therapies other than medications during the observation period, name of therapies
8. Hematological Tests Parameters (Number of white blood cell count, eosinophils in the blood, CRP)
   Test date and results of hematological test at the start of Nucala administration (during 0-4 weeks before the start of Nucala administration), Weeks 12, 24, 36, 48, 60, 72, 84, and 96 after the first dose, or at withdrawal/termination (if test performed)
9. Hematological Tests Parameters (MPO-ANCA* (myeloperoxidase), PR3*-ANCA (proteinase3))
   Test date and results of hematological test at the start of Nucala administration (during 0-4 weeks before the start of Nucala administration), Weeks 24, 48, 72, and 96 after the first dose, or at withdrawal/termination (if test performed)
   *: antineutrophil cytoplasmic antibody, ANCA (antineutrophil cytoplasmic antibody)

10. Clinical symptoms (only disease activity relevant to EGPA in systemic vasculitis*assessed) (9 organ-system (General, Cutaneous, Mucous membranes/eyes, ENT, Chest, Cardiovascular, Abdominal, Renal, Nervous system) and 56 items)
Presence or absence of clinical symptoms and findings (any of 9 organ systems) at the start of Nucala administration (during 0-4 weeks before the start of administration), Weeks 12, 24, 36, 48, 60, 72, 84, and 96 after the first dose, or at withdrawal/termination, date of assessment.
If EGPA-related clinical symptoms or clinical findings in any of the 9 organ-systems were detected, items which corresponds to in each organ-systems will be selected from a total of 56 items.
Additionally, if a sign of exacerbation was observed in above mentioned clinical symptoms or clinical findings when compared to the assessment performed 12 months before this (or more than 12 months before if no assessment was performed within the period), "exacerbation" will also be selected.*: excerpt from BVAS（Birmingham Vasculitis Activity Score）(Vers.3)
11. Exacerbation of bronchial asthma
If a patient has bronchial asthma as a comorbidity, frequency of exacerbation of bronchial asthma which corresponds to the either types defined below and a total number of days patient hospitalized for bronchial asthma treatment from 48 weeks prior to the initiation of Nucala treatment to Weeks 12, 48 and 96 after the administration (or to the time point of withdrawal/termination);
・exacerbation of bronchial asthma which requires hospitalization
・exacerbation of bronchial asthma which requires emergency room visit
・exacerbation of bronchial asthma which requires usage of systemic steroids*
*The standard definitions for the usage of systemic steroids are as follows;
When a patient requires continuous administration of steroids systemically, in concrete terms, orally, intravenously or intramuscularly, for ≥three days. However, as for intramuscular injection, it must also include a continuous administration of dexamethasone phosphate acid ester sodium or betamethazoneline acid ester sodium for ≥three days, or one or more dose of triamcinolone acetonide.
When a patient requires administering systemic steroids double the existing maintenance dose for ≥three days in patients receiving the maintenance therapy of systemic steroids requiring dose increase associated with exacerbation of bronchial asthma.
Multiple exacerbation of asthma for which steroids are administered at an interval of <seven days will be handled as continuation of exacerbation of the same asthma.
12. Hospitalization for EGPA treatment
Presence or absence of hospitalization for EGPA treatment 96 weeks after the administration (or to the time point of withdrawal/termination) during the observation period, date of hospitalization and discharge if patient experienced hospitalization
13. Global assessment of effectiveness
Effectiveness will be comprehensively assessed by any of “effective” or “not effective” at Weeks 12, 48 after the start of Nucala administration, end of the observation period, or at withdrawal/termination, based on the course of subjective symptoms, course of clinical symptoms, etc. from the start date of administration to the end of the observation period. If

effectiveness cannot be determined for some reasons, it should be assessed as "indeterminable" and its reasons should be recorded on the CRF.

14. Continuation status of Nucala
    Continuation status of Nucala at Weeks 12, 48 after the start of administration, end of the observation period, the reason if a patient has withdrawn from/terminated administration
15. Pregnancy
    Whether Nucala is administered to a pregnant woman or not, the presence or absence of pregnancy during the observation period, and the expected delivery date (if a patient is female)
    In addition, the follow-up investigation should be conducted for a mother and her foetus as far as possible regarding the course of delivery, spontaneous abortion, elective abortion, and AEs, etc.
16. Adverse events (AEs)
    Presence or absence of AEs after the start of Nucala administration, diagnosis or symptoms, occurrence date, outcome of AEs, outcome date, seriousness, reason for assessing as serious, relationship to Nucala, factors suspected of being related to AEs other than Nucala
    1) In this study, the safety specifications matters are defined as follows;
       ・Hypersensitivity including Anaphylaxis, Infections, Malignant tumor
    2) To grasp the safety specifications and ADRs, the investigator will collect the information about all AEs (e.g., a disease, symptom, abnormal laboratory value) occurring after the start of Nucala administration on the CRF, regardless of whether or not Nucala is related to an AE. Considering whether or not the possibility of a reasonable relationship to Nucala is present, etc., the relationship to Nucala will be assessed on any of "related" or "not related".
    3) The AEs assessed as "related" to Nucala will be handled as an "ADR" suspected of being caused by Nucala.
17. Follow-up investigation (only in patient who has withdrawn from/terminated due to "symptom improvement")
    Assessment date after the end of follow-up period, presence or absence of AEs leading to death, serious infections, PML, and MT, diagnosis or symptoms, occurrence date, outcome of AEs, outcome date, seriousness, reasons for assessing as serious, relationship to Nucala, factors suspected of being related to AEs except Nucala

9. Analysis Items and Methods

1. Analysis items
   1) Patient disposition-related matters
      i). Number of enrolled patients and number of patients whose CRF is collected and fixed
      ii). Number of patients included in the safety analysis set and number of patients included in the effectiveness analysis set, number of patients excluded from analysis and the reason for exclusion
      iii). Number of patients included in the analysis sets regarding remission and recurrence, number of patients excluded from the analysis sets and the reason for exclusion
   2) Safety-related matters
      i). Occurrence of ADRs/infections (type, severity and incidence of ADRs, etc.)

ii). Factors that potentially affect safety (occurrence of ADRs and infections by patient characteristics, etc.)

iii). Occurrence of events defined as a priority study matters

3) Effectiveness-related matters

i). Responder rate based on global assessment of effectiveness

The responder rate is the proportion of patients assessed as “effective”.

ii). Factors that potentially affect effectiveness (responder rate by patient characteristics, etc.)

iii). Time to EGPA remission and recurrence

The remission and recurrence are defined as follows;

- Remission: BVAS=0 in the assessment of disease activity in systemic vasculitis assessed by 9 organ-system, 51 items.
- Recurrence: If any of the following occurs during the observation period
  - Initiation/increased dose of adrenal cortical steroid
  - Initiation/increased dose of immune-suppressive agent
  - Hospitalization in association with the EGPA treatment

2. Analysis methods

Concerning the items associated with safety and effectiveness, etc., the odds ratio and 95% confidence interval will be calculated for factors that potentially affect them. These will be graphically presented using a forest plot, etc., as appropriate. For comparison of the scores, etc., the mean values and quartile points, etc. for values at the time of measurement and changes from baseline will be calculated.

10. Organizational Structure

Refer to the Attachment 1.

11. Name, Address of the Outsourcees, and the Scope of Outsourced Operations

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12. Scheduled Timing to Be a Milestone for Assessing the Status and Results in the Study or Reporting to the Pharmaceuticals and Medical Devices Agency (PMDA) and Rationale

- At the time of Periodic Safety Reports: consideration will be comprehensively given to the safety and effectiveness information.
- At the time of re-examination application: the final report will be prepared/submitted, based on the results of tabular analysis obtained from the fixed data of all collected CRFs.

13. Additional Measures that Have a Potential to Be Taken Depending to the Study Results and the Decision Criteria for the Start

The RMP, including the following, will be reviewed at the timings to be a milestone.

- Regarding hypersensitivity including anaphylaxisthe, if the proportion of occurrence, peak occurrence period and risk factors become visible as an ADR caused by Nucala, the necessity for revising the Package Insert and study materials will be considered as appropriate.
- Including whether or not a new concern in the safety specification is present, the necessity for changes in the content of plan in the study will be considered.
- The necessity for creation of the Risk Minimization Plan for a new concern in the safety specification will be considered.

14. Publication of the Study Results

The information regarding the results of the study will be provided to clinical sites as an interim report and a final report as appropriate for the purpose of "proper use" and "safety assurance", considering a proper timing and the number of patients whose CRF is collected, etc., by means of presentation at academic conferences and papers.

In addition, the summaries of the plan and results in the study will be disclosed in GSK Clinical Study Register.

15. Other Requirements

1. Protocol revision

   The progress in the study, the number of patients excluded from analysis, occurrence of unexpected/serious ADRs, large increase in occurrence of specific ADRs and validity of the study items, etc. will be timely grasped during the study period, and the Protocol will be reviewed and revised if required.

   If the content of the Protocol in the study has been changed, the Change Notification should be submitted to the PMDA in advance, except for minor changes.
2. Measures to be taken in detecting issues or concerns

If issues, etc. have been detected from the results of assessment/analysis during the study period or after the completion of the study, consideration will be given on whether or not the SDUI or Post-marketing Clinical Study should be newly conducted, as appropriate.

16. Attachments

1) Organizational structure for post-marketing surveillance operations AT1
2) NUCALA Subcutaneous Injection Special Drug Use Investigation (EGPA, long-term) Written Contract AT2
3) NUCALA Subcutaneous Injection Special Drug Use Investigation (EGPA, long-term) Implementation Guidance AT3
4) NUCALA Subcutaneous Injection Special Drug Use Investigation (EGPA, long-term) Enrolment Form AT4
5) NUCALA Subcutaneous Injection Special Drug Use Investigation (EGPA, long-term) Case Report Form 1（From the start of Nucala administration to Week 12） AT5
6) NUCALA Subcutaneous Injection Special Drug Use Investigation (EGPA, long-term) Case Report Form 2（Week 13 to Week 48） AT6
7) NUCALA Subcutaneous Injection Special Drug Use Investigation (EGPA, long-term) Case Report Form 3（Week 49 to Week 96） AT7
8) NUCALA Subcutaneous Injection Special Drug Use Investigation (EGPA, long-term) Case Report Form 4（Follow-up investigation） AT8