Nucala® Subcutaneous Injection
Special Drug Use Investigation
(Long-Term)

Protocol

GlaxoSmithKline K.K.

Revised: 8 December 2022 (Vers.3.1)

<Contents>

1. Objectives

The objective of the study is to collect and assess information regarding the safety and effectiveness of long term use of Nucala® for subcutaneous injection (hereinafter referred to as "Nucala") in asthma patients in daily clinical practice.

2. Safety Specification

In the study, the occurrence of safety specification and the priority investigation matter will be monitored. They will be defined as follows;

- Hypersensitivity reaction including anaphylaxis
- Infections
- Malignant tumour

3. Target Population

The study will include patients receiving Nucala for the first time for treatment of bronchial asthma (a refractory asthma whose symptoms are inadequately controlled despite receiving standard asthma medications), for which Nucala is indicated.

4. Target Sample Size and Rationale

1) Target number of subjects : 1,000 subjects (as enrolled subjects)
2) Rationale :

In the Phase III Global Trial (385 subjects), the incidence of adverse drug reactions (ADRs) occurring in one patient was 0.26%. Since 885 subjects are required to detect an ADRs including unexpected ADRs occurring at an incidence of ≧0.26% in at least one patient with a probability of 90%, the target number of subjects was set at 1,000 in consideration of withdrawal and dropouts.

In addition, in the placebo-controlled trial targeting severe asthma patients, the incidence of "allergic reaction/hypersensitivity", one of the "hypersensitivity reaction including anaphylaxis" defined as the important potential risk, was 1.14% (3/263 subjects). On the assumption that the incidence used as a threshold is assumed to be 1.2%, to confirm the incidence in the post-marketing surveillance with the estimation accuracy which detects the 1.2% of threshold with a statistical power of ≧80% when the real risk exists two times or more of the threshold, 827 subjects are required as a safety analysis set. Accordingly, it is thought to be possible to examine the incidence in the study with 1,000 subjects.

5. Planned Number of Medical Institutions by Department

Approximately 200, mainly the departments of respiratory medicine

6. Study Period

1. Study conduct

Study period : January 2017 - September 2023

Observation period: The observation period per subject will be 1 year (52 weeks) from the initiation of Nucala treatment.

In addition, the follow-up investigation will be conducted for 2 years after the observation period (or after the withdrawal/termination, if a subject has withdrawn from/ terminated the administration of the drug) to examine the occurrence of malignant tumour.

Planned enrollment period : January 2017 - June 2020

However, if the number of enrolled subjects has reached the target sample size, enrollment may be terminated even before completing the above-mentioned planned enrollment period.

2. Study end

Completion of final analysis: January 2024

Completion of final report writing : June 2024

7. Study Methods

In the study, the electronic data capture (EDC) system will be used for case registration and data collection.

1) Request and contract for the study
   (1) The person in charge of the study (medical representative or monitoring outsourcee) will explain the objectives, target population, study items, study methods, etc. to the planned physicians for the study, etc. at the medical institutions where Nucala is adopted/delivered, and will request them to cooperate with the study.
   (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 starting the study.
2) Enrollment of target population

   The study will be conducted using a central enrollment method.
   (1) The investigator will enter and enroll subject information, etc. in the EDC system within 14 days from the initiation of Nucala treatment regarding "3. Target Population" who started administration of Nucala after the conclusion of the contract (the start date of the administration will be regarded as Day 1).
   (2) If the number of enrolled subjects has reached the number of contracted subjects, enrollment into the study will be terminated.
3) Collection of data and entry in the EDC system
   (1) The investigator will confirm the study items, such as the characteristics of enrolled subjects.
   (2) If asthma control test (ACT) is conducted to an enrolled subject at the initiation of Nucala treatment, and at Week 12, 24 and 52 after the administration (or at the time point of withdrawal/termination if a subject has withdrawn from/terminated the administration), the investigator will check the content, and enter the test score in the EDC system.
   (3) During the observation period, the investigator will monitor the information regarding the safety and effectiveness, etc. If an enrolled subject does not visit the hospital/clinic during the observation period, the investigator will monitor the information regarding AEs and others by telephone, etc. as far as possible.
   (4) The investigator will enter the information of the enrolled subjects obtained at the end of the observation period, and send it.
   (5) During the follow-up period of 2 years after the observation period (or after the withdrawal/termination if a subject has withdrawn from/terminated the administration), the information regarding the onset of malignant tumour will be monitored. The investigator will enter the information of an enrolled subject obtained at the time point when the onset of malignant tumour has been monitored or at the end of the follow-up period in the EDC system, and send it.

In case other ADR (AE suspected of being related to Nucala), has been monitored, the investigator will contact the person in charge of the study. If an enrolled subject does not visit the hospital/clinic during the follow-up period, the investigator will confirm the presence/absence of onset of malignant tumour by telephone, etc. as far as possible.

8. Study Items

The investigator will collect the information regarding the following items, etc. as far as possible and enter it in the EDC system.

1) Information regarding medical institutions
   Name of medical institution, department, investigator
2) Subject characteristics (at the initiation of Nucala treatment)
   Identification number, gender, year of birth, start date of administration, hospitalization status, reason for use, presence/absence and name of complications (renal impairment, hepatic impairment, allergy, others), history of smoking, duration of asthma, pre-administration severity and type of asthma
   To protect the confidentiality regarding identification of an individual subject, the identification number should be a unique number assigned to an individual subject by the investigator, etc.
   In this study, any disease/symptom except for asthma which is present before the initiation of Nucala treatment will be handled as a “complication”.
3) Pretreatment medications for asthma (during 4 weeks prior to the initiation of Nucala treatment)
   Presence or absence of pretreatment medications for asthma during 4 weeks prior to the initiation of Nucala treatment, category and product name of medication, single dose and dose unit (as for inhaled steroids and oral steroids)
4) Administration status of Nucala
   Single dose and dose unit, daily dose frequency, date of administration
5) Concomitant medications
   Presence or absence of concomitant medications, name of medications, route of administration, reason for administration, single dose and dose unit of inhaled steroids and oral steroids during the observation period
6) Concomitant therapies for asthma (except for medications)
   Presence or absence of concomitant therapies for asthma, name of therapies during the observation period.
7) Blood test item
   Presence or absence of eosinophils count $\geqq 300/\mu L$ during 52 weeks prior to the Nucala treatment, eosinophils count and examination date at the initiation of Nucala treatment, at Week 12, 24 and 52 after the administration or at the time point of withdrawal/termination (only if examination is performed), administration history of Omalizumab, serum total IgE levels* and examination date
   * In subject with Omalizumab history, the serum total IgE levels measured before the treatment start of Omalizumab or, on and after 1 year post last dose will be entered.
8) Exacerbation of asthma
   Frequency of exacerbation of asthma from 52 weeks prior to the initiation of Nucala treatment to 52 weeks after the administration (or to the time point of withdrawal/termination), frequency of exacerbation of asthma and number of days of hospitalization from 52 weeks prior to the initiation of Nucala treatment to 52 weeks after

the administration (or to the time point of withdrawal/termination) which corresponds to the either types of exacerbation defined below;

・exacerbation of asthma which requires hospitalization

・exacerbation of asthma which requires emergency room visit

・exacerbation of asthma which requires usage of systemic steroids*

*The definitions for use of systemic steroids are as follows;

When administering steroids (e.g., prednisolone) orally and intravenously (or intramuscularly) for a total of ≧three days are required.

When in subject receiving the maintenance therapy of systemic steroids, who requires administering double the existing maintenance dose for≧three days.

Multiple exacerbation of asthma for which steroids are administered at a interval of ＜ seven days will be handled as continuation of exacerbation of the same asthma.

9) Respiratory Function Test (Peak Expiratory Flow (PEF))
Morning/evening PEF score measured at the nearest time point of 1 week before and after the initiation of Nucala treatment, and at Week12, 24, and 54 after the administration, or at the withdrawal/termination* (only if PEF is conducted), measurement date, measurement time of the day, presence and absence of use of short-acting beta 2 agonist (SABA) within 4 hours before measuring PEF score

* All PEF score obtained during this period will be entered in the EDC system

10) Asthma Control Test (ACT)
The information of ACT recorded by a subject at the initiation of Nucala treatment, at Week 12, 24 and 52 after the administration, or at the time point of withdrawal/termination if a subject has withdrawn from/terminated administration. (only if ACT is conducted)

11) Global assessment of effectiveness
Effectiveness will be comprehensively assessed by any of “effective” or “not effective” at 52 weeks after the initiation of Nucala treatment or at the time point of withdrawal from/termination of administration, based on the course of subjective symptoms, and course of clinical symptoms, etc. from the initiation of Nucala treatment to the end of the observation period. If effectiveness cannot be determined for some reasons, it should be assessed as “indeterminable”, and the reason should be entered in the EDC system.

12) Administration of the drug at the end of the observation period
Administration of the drug at the end of the observation period, the reason if a subject has withdrawn from/terminated administration

13) Occurrence of malignant tumour during 2 years after the observation period (follow-up investigation)
Presence or absence of onset of malignant tumour during 2 years after the observation period (or during 2 years after the withdrawal/termination if a subject has withdrawn from/terminated administration of the drug), diagnosis or symptoms, onset date, outcome of malignant tumour, outcome date, seriousness, relationship to Nucala and factors suspected of being related to AEs except for Nucala

14) Pregnancy
(For female subjects) whether or not the drug is administered to a pregnant woman, whether or not a subject is pregnant during the observation period and expected delivery date

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.

15) Adverse Events (AEs)

Presence or absence of AEs after initiation of Nucala treatment, diagnosis or symptoms, onset date, outcome of AEs, outcome date, seriousness, reason for assessing as serious, relationship to the drug, factors suspected of being related to AEs except for Nucala

(1) In this study, the priority study matters are defined as follows;

- Hypersensitivity reaction including anaphylaxis, infections and malignant tumour

(2) To grasp the priority study matters and ADRs, the investigator will enter the information regarding all AEs (e.g., a disease, symptom, abnormal laboratory value) occurring after the initiation of Nucala treatment in the EDC system, regardless of whether or not the Nucala is related to an AE. Considering whether or not the possibility of a reasonable relationship to the drug is present, etc., the relationship to the drug will be assessed on a scale of two categories, any of "related" or "not related", and it will be entered in the EDC system.

(3) AEs assessed as "related" to Nucala will be handled as suspected "ADRs" that are caused by the product.

9. Analysis Items and Methods

1) Analysis items

(1) Subject disposition-related matters

① Number of enrolled subjects and number of subjects whose data is entered in the EDC system and fixed

② Number of subjects included in the safety and effectiveness analysis sets, number of subjects excluded from analysis and the reason for exclusion

③ Number of subjects included in the analysis sets regarding exacerbation of asthma, number of subjects excluded from the analysis sets and the reason for exclusion

④ Number of subjects included in the analysis sets regarding ACT, number of subjects excluded from the analysis sets and the reason for exclusion

(2) Safety-related matters

① Occurrence of ADRs and infections (type, severity and incidence of ADRs, etc.)

② Occurrence of events defined as a priority investigation matter

(3) Effectiveness-related matters

① Response rate based on the global assessment of effectiveness
The response rate is the proportion of subjects assessed as "effective".

② Frequency of exacerbation of asthma

③ Total score of ACT

④ PEF score

2) Analysis methods

(1) Safety

① The incidence of ADRs and 95% confidence interval will be calculated.

(2) Effectiveness

① The response rate and its 95% confidence interval will be calculated.

② For comparison of the scores, etc., the summary statistics for values at the time of measurement and changes from baseline will be calculated.

(3) Consideration of covariates

① The covariate that affects safety (incidence of ADRs) will be considered by calculating the odds ratio and its 95% confidence interval.
② The covariate that affects effectiveness (response rate) will be considered by calculating the odds ratio and its 95% confidence interval (It will be graphically presented using a forest plot, etc., as appropriate).

10. Organizational Structure

See Attachment 1.

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

1) Enrollment
Outsourcee : CMIC Co., Ltd. (1-1-1, Shibaura, Minato-ku, Tokyo)
Scope : patient enrollment and other related operations
2) Data management
Outsourcee : CMIC Co., Ltd. (1-1-1, Shibaura, Minato-ku, Tokyo)
Scope : patient enrollment and other related operations
3) Statistical analysis
Outsourcee : CMIC Co., Ltd. (1-1-1, Shibaura, Minato-ku, Tokyo)
Scope : statistical analysis and other related operations
4) EDC system operarions
Outsourcee : FUJITSU FIP Corporation (1-2-1, Shibaura, Minato-ku, Tokyo)
Scope : development and operation of EDC system, and other related operations
5) Monitoring
Outsourcee: CMIC Co., Ltd.
Shibaura1-1-1, Minato-ku, Tokyo
Scope : contract with medical institutions, payment to medical institutions, promotion of enrolment and CRF collection, other related operations

12. Planned 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 in the EDC.

13. Additional Measures that Have a Potential to Be Taken Depending on 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 anaphylaxis, if the proportion, the peak onset period and risk factors become visible as an ADR caused by the drug, the necessity for revision to the Package Insert and study materials will be considered as appropriate.
- Including the presence or absence of a new issue in the safety specification, the necessity for changes in the content of plan in this study will be considered.

· The necessity for creation of Risk Minimization Plan for a new issue 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 subjects whose data is collected, etc., by means of presentation at an academic conference and papers.

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

15. Other Requirements

1) Protocol Revision

The progress in the study, the number of subjects 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.

<Examples of minor changes>

(1) Change of the organization or the person in charge for the conduct of the study

(2) Change of the planned number of medical institutions (by department)

(3) EDC system

[1] Modifications to the layout of items (relocation of items, enlargement or reduction of sections)

[2] Change in the explanation of items

[3] Inclusion of additional examples of ADRs, in association with a revision of the Precautions or inclusion of noteworthy ADRs

(4) Addition, change, and deletion of items that have no impact on the entire study, particularly efficacy and safety analyses

(5) Study period

[1] Change of the start day of the study due to a delay in the product launch

[2] Prolongation of the study period to correspond to a short-term (within 3 months) prolongation, if necessary, of the registration period

[3] Reduction of the study period in case no change has been made to the planned sample size

2) Handling of problems or questions detected

If any problem is found during the study period or in the evaluation and analysis results, etc. after completion of the study, implementation of an additional special drug use investigation or post-marketing clinical study will be considered according to need.

16. Attachments

5)	Nucala® for Subcutaneous Injection SDUI Case Report Form (CRF)	AT 5
6)	Nucala® for Subcutaneous Injection SDUI Asthma Control Test (ACT)	AT 6