Nucala ® Subcutaneous Injection

Drug Use Investigation

(long-term)

Statistical Analysis Plan

Title : Nucala Subcutaneous Injection Drug Use Investigation (Long-term)

Protocol No. :204524

Version :10.0

Date : 21/SEP/2023

Author : PPD

Study Accountable Person/ Non-Interventional Study Scientific Lead: PPD

Approved by : PPD

Signature/Date

PPD (Statistical) (based on GPSP-WI-P020-10)

Real World Data Analytics

Approved by : PPD

Signature/Date

Functional line manager of Study Accountable Person/ Non-Interventional Study Scientific Lead,(based on VQD-WI-048285(Link))

VEO Respiratory

Table of Contents

1. Purpose of Investigation

This survey was conducted to collect and evaluate the long-term safety and effectiveness of Nucala ® for Subcutaneous Injection (drug) in subjects with bronchial asthma.

2. Software and dictionary to be used

2.1. Statistical analysis and tabulation software

	Software and Version
OS	Microsoft Windows 10 Or use a later version.
Statistical analysis software	SAS Ver.9.4 Or use a later version.
Tabulation software	Microsoft Excel 2016 Or use a later version.

2.2. Dictionary to use

Selected item	Dictionary name
Name of disease (complication), adverse event, and adverse reaction	Calculated based on the version of MedDRA/J used for coding in DM. *The version of MedDRA to be used will be discussed and determined by the team for each report.
Pharmaceutical name, drug name	Prescription Drug Names Data File (to be tabulated in the version used for coding in DM. *As a rule, the most recent version is used.)

3. Defined Terms

Term	Definitions
Date of initiation of drug treatment	The earliest date of medication in CRF [drug administration status]. However, the determination will be made based on the record that both "dose per dose [mg/dose]" and "number of doses per day [doses/day]" in CRF [drug administration status] are not missing.
Date of completion of drug administration	TCRF [Drug administration status] Among the dates listed on the drug administration date, the latest administration date excluding blank dates. However, the judgment will be made based on records in which both the "dose [mg/dose]" and "number of doses per day [doses/day]" of CRF [drug administration] are not missing.
Date of discontinuation of drug	The end date of administration shall be the end date of administration for any case that is determined to be discontinued during the observation period in ``4.11 Handling of discontinued/completed cases and continued cases."
ACT	Asthma control test
IDSL	Integrated Data Standard Library

Term	Definitions
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
LLT	Lower MedDRA/J term
PT	MedDRA/J preferred term
HLGT	MedDRA/J high-group term
SOC	System MedDRA/J Organ Class
SMQ	Standardised MedDRA queries
Ethical drug name data file	Drug data base provided by MT Council
Registration slip	Registry forms collected in EDC.
Case Report Form (CRF)	Case Report Form collected in EDC.
Re-examination period	March 28, 2016-March 27, 2024
Data lock date	The last day of each investigation unit period is defined.
Observation period	One year (52 weeks) from the date of initiation of drug treatment.
Duration of follow-up	The annual will be 2 years (104 weeks) from the date of completion (discontinuation) of drug administration.

4. Handling of cases and data

4.1. Number of subjects

✧ Number of subjects: Number of subjects who met the relevant conditions.

✧ Number of subjects with adverse events (adverse drug reactions):

An adverse event (adverse reaction) is considered an adverse event (adverse reaction) if it occurs in at least one case. When summarizing adverse events (adverse drug reactions) according to symptoms, the following procedures will be performed.

・For each SOC, the same SOC in the same case is counted as a single case.

・For each PT, the same PT in the same case is counted as a single case.

Adverse events occurring outside the investigation period or beyond the observation period for each patient are not included in this investigation.

4.2. Analysis set/site

Selected item	Definitions
Enrolled sites	Sites for all enrolled subjects (eligible subjects). Institutions with subjects with a registration date and before the data lock date (excluding duplicate site codes).
Enrolled subjects	Subjects registered within the enrollment period specified in the protocol (January 1, 2017, to June 30, 2020) (enrolled eligible subjects). Subjects with a registration date before the data lock date.
Sites that have obtained a CRF	All registry sites for which case report forms were collected. "Case report form status" in the case report form information of PMS progress control system is one of the following: "This approval", "Survey sheet re-survey", "Content confirmation", "Content confirmation", "Re-entry", "Re-investigation after approval", and "Confirmation after approval" Institutions with a value on the date of receipt of the survey form headquarters and a date prior to the data lock date
Subjects that have obtained a CRF	Among the enrolled subjects, all subjects for which a case report form was collected. Case of the case report form recalled in the above-mentioned "case report form recalled site"
Sites that have fixed a CRF	Of the case report form collection sites, those where the case report form was approved. Institutions where "case report form status" is "approved" in the case report form information of PMS progress control system. Institutions with values on "the approval date of this case report form" and dated before the data lock date
Case that have fixed a CRF	Of the enrolled subjects, all subjects in which the case report form was retrieved and fixed. Subjects in which PMS Progress Control System-based case report form information includes the date of recall, the date of completion of treatment, and the date of completion of treatment is before the date of data lock.
Sites for safety analysis	Of the CRF fixed sites, subjects that do not fall under the safety analysis exclusion subjects (see 4.3.1).

Selected item	Definitions
Safety analysis subjects	Of the subjects fixed in the CRF, subjects that do not fall under the safety analysis exclusion subjects (see 4.3.1).
Effectiveness analysis subjects	Of the subjects included in safety analysis, subjects that do not fall under the subjects excluded from efficacy analysis (see 4.3.2).
Follow-up analysis subjects	Of the subjects s included in safety analysis, subjects that a follow-up survey was conducted 52 weeks after the end of observation (or after discontinuation of administration if this drug was discontinued), and a questionnaire was collected.
ACT analysis subjects	Of the subjects s included in effectiveness analysis, Subjects that ACT scores were measured before and after starting administration of this drug
Asthma exacerbation analysis subjects	Of the subjects s included in effectiveness analysis, Subjects that asthma exacerbations were count before and after the start of administration of this drug.

4.3. Analysis exclusion criteria

4.3.1. Subjects excluded from safety analysis

If the reasons for exclusion overlap and prioritize, the reasons for exclusion from safety analysis should be assigned according to the following ranking:

Code	Safety Reasons for the exclusion from analyses	Priority Ranking	Condition of exclusion	Logic Judgement
S1	Outside the period of investigation and registration	1	・The date of commencement of drug administration or the date of completion of drug administration is outside the investigation period. ・The registration date is outside the registration period.	○
S2	Outside the contract period	2	・The date of commencement of drug administration or completion of drug administration is outside the contract period. ・The registration date is outside the contract period.	○
S3	Violation of registration	3	Not registered within 14 days of the starting day of drug administration	○
S4	Patients not treated	4	Subjects in which the administration status of drug is not described at all, or in which the description of all doses is 0	○
S5	No visit after the first administration date	5	[drug administration status at the completion of the run-in period]. The reason for discontinuation/completion of administration is "no visit after the first administration date"	○
S6	Adverse event data unknown	6	The presence or absence of adverse events is blank, and there are no adverse event data.	○
S7	Other (safety)	7	Subjects for whom the reasons for exclusion from the safety analysis were other than the above (S1～S6)	×

4.3.2. Effectiveness analysis excluded subjects

If the reasons for exclusion overlap and prioritize, the reasons for exclusion from effectiveness analysis will be assigned according to the following ranking:

Code	Effectiveness Reasons for the exclusion from analyses	Priority Ranking	Condition of exclusion	Logic Judgement
E1	Off-label use	1	If the reeasons for use is other than bronchial asthma.	×
E2	Response not evaluable	2	[Overall effectiveness evaluation]. ""Undeterminable"."	○
E3	Response evaluation not described	3	[Overall effectiveness evaluation]. There is no entry.	○
E4	Other (effectiveness)	4	Subjects for whom the reason for exclusion from effectiveness analysis was other than the above (E1～E3)	×

4.3.3. Other subjects excluded from analysis

Not applicable in this survey.

4.4. Handling of missing data

4.4.1. Data complement

Data imputation is not performed for missing data.

4.4.2. Missing continuous quantities

Missing data from the tabulation of serial quantities are excluded from the tabulation. If there is a continuous volume of data at more than one time point, only missing time points are excluded. In classifying continuous quantities into categorical categories, follow 4.4.3 Categorical Data.

4.4.3. Categorical data

✧ Handling of Unknown Categories

Depending on whether the category contains an unknown category, it should be labeled as follows:

- When the category includes unknown categories

  Missing or undescribed data are not distinguished, and if present in one case, they are labeled as "undescribed".

  When 0 subjects fall under "unknown" or "undescribed", the category is not labeled.

- If the category does not contain an unknown category

  Missing/unknown/undescribed subjects are not distinguished, and if relevant subjects exist, they are labeled as unknown.

  When 0 subjects fall under "unknown," the unknown category is not output.

✧ Missing data are included in the denominator of proportions.

✧ Exclude unknown categories when calculating tests and odds ratios

4.4.4. Date variable

The imputation of date variables is addressed as follows.

<Date of completion of drug administration>

✧ If there is a deficiency date, it is not imputed and is considered unknown.

<Adverse events>

✧ If there is a defect on the date of onset or the date of outcome, it is not imputed and is considered unknown.

4.5. Handling of presence/absence

Whether or not such information is handled shall be as follows in principle.

Description of the presence/absence column	Presence or absence of detail field records	Handling of presence/absence
Absence	Absence	"Absence" is set.
	Presence	"Presence" is defined.
Presence	Absence	"Unknown" is defined.
	Presence	"Presence" is defined.
Unknown/Not stated	Absence	"Unknown" is defined.
	Presence	"Presence" is defined.

4.5.1. Presence or absence of pregnancy

Regarding pregnancy status ,the decision is made as follows when the gender is "female".

✧ If you enter "Yes" in "Pregnancy" in CRF, it will be counted as "Pregnant".

✧ If you enter "no" in "pregnancy" in CRF, it will be counted as "no pregnancy".

✧ If "Pregnancy" in the CFR does not have "Yes" or "No" entered, it will be counted as "Unknown Pregnancy".

4.5.2. Presence or absence of prior medication

All drugs entered on the page of the case report form [Pretreatment Drugs for Bronchial Asthma] are included.

✧ Determination of the presence

The presence or absence of the previous drug, the category of the drug, and the name of the product will be determined in the following order.

① When the item "Product name (only for the most recent use)" in the case report form [Pre-treatment drugs for bronchial asthma]

1. If the product name (only for the most recent use) in the [Pretreatment Drugs for Bronchial Asthma] in the case report form is entered, the product name is "present"
2. 1. If there is at least one entry in the product name (only for the most recent use) of the [Pretreatment Drugs for Bronchial Asthma] in the case report form, the drug category to which the product name is applicable is "present"
3. 1. Or product name or drug category not applicable in 2. shall be "nothing

② When there is no item in the product name (only the most recently used drug) of the case report form [Pre-treatment drug for bronchial asthma]

1. If the "Drug category (multiple choices) of the case report form [Pre-treatment Drugs for Bronchial Asthma] is entered, the corresponding

drug category is "presence"

2. 1. Drug categories not applicable are designated as "nothing

③ Determination of the presence or absence of pretreatment drugs

1. "Present" if one or more drug categories fall under ①-2 or ②-1

2. 1. When it does not correspond, it is considered as "nothing."

4.5.3. Presence of concomitant medications

All drugs entered on the [Combination Drugs] page of the case report form are included.

✧ Determination of the presence

The presence or absence of concomitant medication will be determined as follows.

- If the "Drug name" in the [Combination Drug] section of the case report form is entered, it shall be "presence"
- In other subjects than the above, it is set to "nothing"

4.5.4. Presence or absence of concomitant therapy

All therapies entered on the page of the case report form [Combination therapy for bronchial asthma (other than drugs)] are included.

✧ Determination of the presence

Concomitant therapy is assessed as follows.

- "Presence" is indicated in "Therapy name" in the survey form [Combination therapy for bronchial asthma (other than drugs)].
- In other subjects than the above, it is set to "nothing"

4.5.5. Presence of complications

All events entered in the disease name of the complication on the [Patient Background] page of the case report form are included.

✧ Determination of the presence

The presence or absence of complications is determined as follows.

- "Presence" is indicated when the "disease name (including allergy history)" in the [Patient background] of the survey form is entered.
- In other subjects than the above, it is set to "nothing"

4.6. Calculation of days and age

✧ Days

The number of days based on the starting day of drug administration is calculated as follows, when the study day is before or after the starting day of drug administration.

・Date of first administration of drug < = date of study: date of subject-date of first administration of drug + 1

・Date of first administration of drug > target date: target date-drug starting date

※Days (days) after the initiation of drug treatment are labeled as 1 for the first day of drug treatment and-1 for the day before the initiation of drug treatment; 0 is not used.

Treat 1 week as 7 days.

The definition of each period shall be as follows.

Selected item	Definitions
Duration of drug treatment (days)	Calculate using the following formula. Calculation formula Duration of drug treatment (days) = date of completion of drug treatment-date of initiation of drug treatment + 1
Time to onset of adverse drug reactions (days)	Calculate using the following formula. Calculation formula Day of onset of adverse drug reaction-Day of first administration of drug + 1

✧ Age

Age [years] is calculated using the date at the beginning of drug treatment, complemented with June 30 in the birth year on the [cover] of the case report form.

① If the year (Taisho, Showa, and Heisei) is entered in the 'year of birth' on the [cover] of the case report form, it is converted to the western calendar and used to calculate the age.

If there is a western calendar entry in the 'year of birth' on the [cover] of the case report form, it will be used to calculate age as in.

② Determine the difference in the year of the date.

③ When the date of birth is before the date of birth, subtract 1 from the difference of the year to reach the age.

When the date is the same or later than the date of birth, the difference between the years is set as the full age.

4.7. Assessment window

4.7.1. Adoption data for blood test items by assessment period

✧ Adoption data for the evaluation period of blood eosinophil count

Identify Adoption data in the following processing order:

① Laboratory data that are unknown or cannot be quantified are excluded.

② In accordance with the table below, the data for inclusion will be identified according to the time of evaluation.

Time of evaluation	Adoption data
9-52 weeks prior to initiation of drug	Blood eosinophil count [/μL] entered in the "9-52 weeks prior to drug administration" section of the case report form [blood test items-blood eosinophil count]
At the beginning of drug administration	Blood eosinophil count [/μL] entered in the entry column for drug administration (0-8 weeks prior to administration) in the [Blood test items-Blood eosinophil count] in the case report form
12 weeks after initiation of drug	Blood eosinophil count [/μL] entered in the "12 weeks after the initiation of drug administration" section of the case report form [blood test items-blood eosinophil count]
24 weeks after initiation of drug	Blood eosinophil count [/μL] entered in the "24 weeks after the start of drug administration" section of the case report form [blood test items-blood eosinophil count]
52 weeks after the initiation of drug administration or at the time of discontinuation/completion of administration	Blood eosinophil count [/μL] entered in the "Week 52 after initiation of drug treatment or at the time of discontinuation/completion" section of the case report form [blood test items-blood eosinophil count] However, if there is no entry in the "Week 52 after the start of drug administration or at the end of administration" section of the [Blood test items-Blood eosinophil count] of the case report form in subjects who discontinued/completed the study, the following adoption data will be specified. Blood eosinophil counts [/μL] entered in the [blood test items-blood eosinophil counts] of the case report form after 12 weeks of drug administration, and the blood eosinophil counts [/μL] at the latest assessment period ※In subjects who continue for 52 weeks, the treatment will be handled as "52 weeks after the initiation of drug therapy."

✧ Adoption data for evaluation time of serum total IgE concentration

Identify recruitment data in the following processing order:

① Laboratory data that are unknown or cannot be quantified are excluded.

② In accordance with the table below, the data for inclusion will be identified according to the time of evaluation.

Time of evaluation	Adoption data
Prior to start of drug	Serum total IgE level entered in the "Prior to drug administration" section of the case report form [blood test item-serum total IgE level] [IU/mL]

4.7.2. Adoption data for effectiveness endpoints by time point

✧ Adoption data for the time of evaluation of exacerbations of asthma

Identify recruitment data in the following processing order:

① Exclude unknown or non-quantifiable input data.

② In accordance with the table below, the data for inclusion will be identified according to the time of evaluation.

Time of evaluation	Adoption data
52 weeks prior to initiation of drug	The data entered in the field "52 weeks prior to the initiation of drug administration" in the [Asthmatic exacerbation] of the case report form
52 weeks after initiation of drug treatment or until discontinuation	Data entered in the field "52 weeks after initiation of drug treatment or until discontinuation of treatment" in the [Asthmatic exacerbation] of the case report form **Entry items of interest** ・ Number of asthma exacerbations ・ Asthma exacerbations requiring hospitalization ・ Total hospital stay ・ Asthma exacerbations requiring emergency department visits ・ Asthma exacerbations requiring use of systemic corticosteroids

✧ Range of adoption of evaluation time for respiratory function test (peak flow)

Data from each evaluation period will be collected from the range of inclusion specified in the table below. If observations or measurements have been performed more than once within the data range, the following procedures will be used to determine the data to be used.

① Adopt data in which "measurement time-period" and "short-acting β_2 stimulant use or not" with input to [respiratory function test (peak flow)] of the case report form are not missing, and the value of "peak flow (PEF)" can be quantified.

② Adoption of data corresponding to the inclusion range category at each evaluation period on the measurement date of the [respiratory function test (peak flow)] in the case report form.

③ For the data adopted in ②, the mean value of the [respiratory function test (peak flow)] peak flow (PEF) value of the case report form is calculated for each recruitment category and used for tabulation.

Mean values are calculated using the following equation.

Mean = total of the peak flow (PEF) values in each recruitment category

÷ Number of records corresponding to each adoption range category

Time of evaluation	Category of scope of adoption
At the beginning of drug administration	Day of first drug dose ≦ ≦ drug Day 7
12 weeks after initiation of drug	Starting day of drug administration +77 days ≦ ≦ drug starting day +91 days
24 weeks after initiation of drug	Day of first drug administration + 161 days ≦ ≦ drug day of first administration + 175 days
52 weeks after initiation of drug	Day of first drug administration + 357 days ≦ ≦ drug day of first administration + 371 days
Discontinuation/completion of drug treatment	End of observation (Week 52)-Day 7 ≦ ≦ End of observation (Week 52) + Day 7

e.g., calculation of the mean peak flow at the beginning of drug treatment

Original data

Case No.	Date of initiation of drug treatment	Days measured	Measurement Time of day	Peak flow (PEF	Use of short-acting β_2 agonists	Data Acceptance *
PPD	2018/3/7	2018/2/10	In the morning	250	With	Non-adoption
		2018/2/10	At night	270	With	Non-adoption
		2018/3/4	In the morning	290	With	Adoption
		2018/3/4	At night	300	With	Adoption
			In the morning	280	None	Non-adoption
		2018/3/2		280		Non-adoption
		2018/3/2	At night	300	None	Adoption
		2018/3/7	In the morning	290	None	Adoption
		2018/3/7	At night	350	None	Adoption

* "Respiratory function test (peak flow)" in the case report form is not missing for both "measurement time period" and "short-acting β_2 stimulant use" and the value of "peak flow (PEF)" can be quantified, and "measurement date" falls within the inclusion category for each assessment period.

Calculation of mean peak flow (PEF

Calculated by (290+300+300+290+350) ÷5.

✧ Adoption of the Asthma Control Test (ACT) at the time of assessment

Identify recruitment data in the following processing order:

① Total scores that are unknown or cannot be quantified are excluded.

② In accordance with the table below, the data for inclusion will be identified according to the time of evaluation.

Time of evaluation	Adoption data
At the beginning of drug administration	Total scored [dots] entered in the entry column for "Initiation of drug administration" in the [Asthma Control Test (ACT)] of the case report form
12 weeks after initiation of drug	Total scored [dots] entered in the "12 weeks after initiation of drug administration" field of the [Asthma Control Test (ACT)] in the case report form
24 weeks after initiation of drug	Total scored [dots] entered in the field "24 weeks after starting drug administration" in the [Asthma Control Test (ACT)] of the case report form
52 weeks after initiation of drug	Total scored [dots] entered in the field "52 weeks after starting drug administration" in the [Asthma Control Test (ACT)] of the case report form
Discontinuation/completion of administration	Total scored [points] entered in the entry column for "Discontinuation/End of Treatment" in the [Asthma Control Test (ACT)] of the case report form However, if there is no entry in the "Discontinuation/End" section of the [Asthma Control Test (ACT)] of the case report form in subjects who discontinued/completed the study, the following inclusion data will be specified. ・ Within the total score [points] entered in the [Asthma Control Test (ACT)] of the case report form, the total score [points] of the latest assessment time among the data from 12 weeks after the initiation of drug treatment.

4.8. Handling of transferred subjects

Not applicable in this survey.

4.9. Adverse events/adverse reactions

Term	Definitions
Adverse Event	Events entered into Argus.
Side Effects	Adverse events other than "Determined causality" and "Reported causality" are "Unrelated" or "Can be denied."
Serious adverse events (adverse drug reactions)	Adverse events (adverse drug reactions) that are "serious."
First adverse event (adverse reaction)	Adverse events (adverse drug reactions) with the date of onset being the earliest event. However, when the onset date includes an unknown event, the following measures should be taken. **When the decision is made in the same case and in the same event unit** Records with unknown date of onset shall be adopted when there is a record containing unknown date of onset. **When judging on a case basis** When an event with an unknown onset date exists after the first adverse event (ADR) is determined in the same case and by the same event unit, the onset date of the first adverse event (ADR) in that patient is unknown.
Adverse reactions after completion of drug administration	Adverse drug reactions are defined as those that meet the following conditions. **Judgment condition** Date of completion (discontinuation) of drug administration < date of onset However, when the date of onset is unknown, it is not subject to evaluation (not applicable) because the condition cannot be judged.

4.10. Safety Specification, Definition of Complications

The following adverse events will be defined for the Safety Specification:

Classification of Safety Specification	Definitions	Dictionary code
Hypersensitivity such as anaphylaxis	Anaphylactic response (SMQ, narrow zone)	20000021(narrow area)
	Hypersensitivity (SMQ, narrow zone)	20000214(narrow area)
Infectious Disease	Infectious diseases: Infectious and parasitic diseases (MedDRA/J SOC)	MedDRA/J SOC:10021881
Malignant tumor	Malignancy (SMQ narrow zone)	20000227(narrow area) 20000228(narrow area)
	Malignant lymphoma (narrow SMQ spectrum)	20000215(narrow area)

In the item of the case report form [patient background] Complications, it is classified according to the following dictionary code.

Classification of complications	Definitions	Dictionary code
Kidney dysfunction	Nephropathy (HLGT)	MedDRA/J HLGT:10029149
	Renal impairment (excl nephropathy) (HLGT)	MedDRA/J HLGT:10038430
	ACUTE RENAL FAILURE (SMQ, broad/narrow spectrum)	20000003(broad and narrow)
Liver dysfunction	SMQ level 1 PT included in "Hepatic disorders" minus SMQ level 3 PT included in "Coagulation and hemorrhage disorders related to the liver"	SMQ level-1 'hepatic impairment': (20000006,20000007,)20000008,20000009,20000010,20000011,20000012,20000013,20000014,(20000015,)20000016,20000017,20000018,20000208,20000209 SMQ Level-3 Coagulation and Hemorrhage Disorders Associated with the Liver: 20000015
Allergy	Allergic diseases (HLGT)	MedDRA/J HLGT:10001708
Other	An event that does not correspond to renal or hepatic dysfunction or allergy.	-

4.11. Handling of Continued/Discontinuation・Completed Administration

Treat as follows:

Continuation of drug treatment (Case report form)	Date of completion of drug administration	Handling (Logic assessment of drug administration)
Continuation of treatment	Date of completion of drug administration-drug administration start day + 1 < 364-28	Treat as discontinued or completed subjects The reason for discontinuation/completion of administration is "unknown"
	Date of completion of drug administration-drug administration start day + 1 > = 364-28	Continued administration (not changed)
Discontinuation/completion of administration	Date of completion of drug administration-drug administration start day + 1 < 364-28	Discontinuation/completion of administration (no change)
	Date of completion of drug administration-drug administration start day + 1 > = 364-28	Treatment is treated as a continuation case, and the reason for discontinuation/completion of treatment as described in the case report form is not used.

✧ The end of observation (Week 52), start/end of follow-up, and last observation day shall be handled as shown below.

Term	Definitions
End of observation (Week 52)	Calculate using the following formula. ・Day of completion of drug administration-drug day of initiation +1 > = 364 End of Observation (Week 52) = +364 on the starting day of drug administration. ・Date of completion of drug administration-drug administration start day + 1 < 364 End of Observation (Week 52) = end of drug administration + 28. However, when the day of completion of drug administration + 28 > drug administration start day + 364, the day of completion of drug administration observation = the day of initiation of drug administration + 364.
Start date of follow-up	・ Date of completion of drug administration-drug administration start day + 1 > = 364 Starting day of follow-up = end of observation (week 52) + 1. ・ Date of completion of drug administration-drug administration start day + 1 < 364 The starting date of follow-up = the date of completion of drug administration + 1.

Term	Definitions
End of follow-up	The following is calculated using "Have you completed the follow-up survey" in the survey form [Confirmation of completion of the follow-up survey]. ・If yes is selected End of follow-up = start of follow-up day + 52 weeks (= 52 × 7 days) × 2-1 ・If yes is not selected ① When the presence or absence of malignancy is "Present" The date of the end of follow-up = the latest in the status of malignancy (follow-up) 2 years after the end of the observation period]. However, if the above date exceeds "the start date of follow-up + 52 weeks (= 52 × 7 days) × 2-1", then "the start date of follow-up + 52 weeks (= 52 × 7 days) × 2-1". ② When the presence or absence of malignancy is "none" End of follow-up = end of drug treatment If the follow-up form has not occurred, the date of completion of follow-up = starting date of follow-up.
Last day of observation	Define as below. ・When focusing on events other than malignancy Final observation day = end of observation day (week 52). ・When focusing on malignancy ① Final observation day = end of follow-up day. ② If the follow-up form has not occurred, the date of last observation = end of observation (52 weeks).

4.12. Handling of subjects whose administration purpose has been changed

The date of the last administration of drug for severe asthma is the date of completion of drug therapy for subjects who have been changed from severe asthma to eosinophilic polyangiitis granulomatosis (EGPA).

5. Items related to statistical processing

5.1. Summary statistics

The number of subjects, mean, standard deviation, minimum, 25% point, median, 75% point, and maximum are indicated.

5.2. Change, Percentage Change, and Percentage

Change from baseline, percentage change, and percentage change are calculated by the following equation.

- ✧ Change = Measured at each observation period-Baseline
- ✧ Percentage change (%) = (Change/ Baseline Measured) × 100
- ✧ Percentage (%) = (number of subjects included/number of subjects included in the analysis) × 100

5.3. Display of results

The labeling of the tabulated results is as follows.

Classification	Labeled digit
Percentage change	The second decimal point is rounded and displayed up to the first rank.
Number of subjects	You display as an integer.
Mean, SD, 25 percentage points; Median, 75 percentage points; confidence interval of the mean	Rounded down to the nearest two digits of the original data and displayed down to the lowest one digit of the displayed digit.
Min, max	Rounded off one digit of the number of digits displayed on the original data and displayed up to the same number of digits as the number of digits displayed.
p value	The fourth decimal point is rounded and displayed up to the third decimal point. However, if the p-value before rounding is less than 0.001, it is labeled as uniformly "p<0.001". If p-value cannot be calculated, p-value shall be "-" (double-byte hyphen). <Example> Original value: 0.0098 Displayed: p = 0.010
Odds ratio; confidence interval of odds ratio; correlation coefficient	The fourth decimal point is rounded and displayed up to the third decimal point.

5.4. Exploratory analysis of influential factors

CCI

[redacted]

6. Primary analysis item

6.1. Case composition

6.1.1. Case Composition (Figure1.01)

Analyses included: -

Analysis content: The following numbers of subjects, the number of subjects excluded, and the reasons for exclusion are shown using a flow chart.

If there are multiple entries in the same case, the reasons for exclusion will be aggregated into high priority exclusion reasons.

The number of sites will be tabulated on a per-site basis, not considering clinical departments.

Figure1.01

- Enrolled sites
- Enrolled subjects
- Subjects that have not obtained a CRF
- Sites that have obtained a CRF
- Subjects that have obtained a CRF
- Subjects where CRF is not fixed
- Sites that have fixed a CRF
- Case that have fixed a CRF
- Subjects excluded from safety analysis and reasons for exclusion
- Number of sites
- Safety analysis subjects
- Effectiveness analysis excluded subjects and reasons for exclusion
- Effectiveness analysis subjects

Figure1.02

- Sites for follow-up
- Follow-up subjects
- Subjects with no follow-up form obtained
- Follow-up case report form collection site
- Follow-up form obtaineded subjects
- Unfixed follow-up form
- Follow-up form fixed site
- Follow-up form fixed subjects

6.2. Patient characteristics and baseline characteristics

6.2.1. Patient characteristics (Table1.01)

Analyses included: Safety analysis subject / Effectiveness analysis subjects

Analysis content: The number of subjects and percent and/or summary statistic will be calculated for each patient characteristics analysis.

The denominator of the constituent ratio (%) is the sum of the subjects included in the respective analyses, unless otherwise stated.

The 25% and 75% points of the summary statistics are not calculated.

Dose is defined as follows.

Pretreatment

1. Excluding missing or incompletely dated drug administration dates in the case report form [drug administration status].
2. The number of daily doses [times/day] in the case report form [drug administration status] excludes missing records.
3. The single dose [mg] of the case report form [drug administration status] excludes missing records.

Selected item	Definitions
Total number of doses [times]	The total number of daily doses [times/day] is used.
Total dose [mg]	For each record of "dose per dose [mg] and "number of daily doses [times/day], the "dose per dose [mg] x "number of daily doses [times/day]" will be calculated, and the calculated data will be summated.
Duration of drug treatment [days]	Use "Duration (days) of drug" in "Calculation of 4.6 Days/Age".
(total) dose to onset of adverse reaction [mg]	For each record on the [drug dosing status] in the case report form that meets the criteria for the date of onset of adverse drug reactions ≧ drug dosing date, the "dose per dose [mg] × "number of daily doses [times/day]" is calculated, and the sum of these calculations is used.
Number of administrations until the onset of adverse drug reactions [times]	The sum of the number of daily doses [times/day] for each record on the [drug dosing status] of the case report form that meets the criteria for the date of onset of adverse drug reactions ≧ drug dosing date.

Patient characteristics items: Table1.01.1:

- Gender: Male, Female, Unknown
- Presence of pregnancy "Women only": None, present, unknown
- Age 1 (years): <15, 15≦ to <65, 65≦ to <75, 75≦, unknown and summary statistics
- Age 2 (years): <65, 65≦, unknown

- Age 3 (years): <12, 12≦ to <18, 18≦, unknown
- Hospitalization/outpatient category: inpatient, outpatient, unknown
- Reasons for drug use: bronchial asthma. Otherwise unknown
- Reasons for drug use and breakdown (name of illness)
- Complications: None, Yes
- Complications (renal dysfunction, hepatic dysfunction, allergy, etc.): None, Yes
- Smoking history: no smoking history, current smoking, current smoking, unknown smoking history
- Primary disease (disease duration): ≦2, 2< to ≦5, 5< to ≦10, 10<, unknown
- Primary disease (severity before administration): mild intermittent, mild persistent, moderate persistent, severe persistent, and most severe persistent
- Primary disease (pathotype): atopic type, non-atopic type, unknown
- Blood eosinophil count (9-52 weeks prior to initiation of drug): <150, 150≦-<300, 300≦-<500, 500≦, unknown and summary statistic
- Blood eosinophil counts (start drug): <150, 150≦ to <300, 300≦ to <500, 500≦ and summary statistic
- History of omalizumab use: None, Yes
- Pretreatment Drugs for Bronchial Asthma: None, Yes
- Concomitant drugs: None, Yes
- Combination therapy (other than drugs) for bronchial asthma: None, Yes

Table 1.01.2: Miscellaneous Complications
Table1.01.3: Treatment Drugs
(The incidence of adverse reactions and the active proportion are also displayed.)
Table1.01.4: Concomitant Drugs and Therapies
(The incidence of adverse reactions and the active proportion are also displayed.)
Table1.01.5: Administration status
(The incidence of adverse reactions and the active proportion are also displayed.)

6.3. Safety evaluation

6.3.1. Inventory of adverse drug reactions by patient characteristics (Table2.01)

Analyses included: Safety analysis subjects

Analysis content: The number of subjects surveyed, the number of subjects with adverse drug reactions, and the incidence proportion of adverse drug reactions and their 95% confidence intervals will be calculated for each patient characteristics.

The incidence of adverse reactions is calculated according to the following formula.

Incidence of adverse drug reactions = number of subjects with adverse drug reactions/number of subjects surveyed for each background item × 100

The number of subjects with adverse drug reactions is counted as 1 patient with at least 1 adverse drug reaction.

Patient characteristics items: Same section as "6.2.1 Patient characteristics (Table1.01)"

6.3.2. Time to onset of adverse drug reactions (Table2.02)

Analyses included: Safety analysis subjects

Analysis content: Regarding adverse reactions, the following items are calculated for each category of time to onset of adverse reactions and the total number of subjects.

- Number and percentage of subjects with adverse drug reactions
- Cumulative number of subjects with adverse drug reactions and the percentage

The denominator of the proportion of each item is as follows:

- Percentage of subjects with adverse drug reactions: Total number of subjects with adverse drug reactions
- Cumulative incidence of adverse drug reactions: total number of subjects with adverse drug reactions

However, the total number of subjects with adverse drug reactions should include "unknown" in the period to onset of adverse drug reactions.

The number of subjects with adverse reactions by SOC and PT will be summarized in terms of the time to onset by category and the total number of subjects.

For the total number of subjects, the percentage will be calculated.

The denominator of the proportion is the number of subjects included in the safety analysis.

Time to onset of adverse reaction

The tabulation of the time to onset of adverse drug reactions is as follows.

- In the tabulation of time to onset of adverse drug reactions by category, each time to onset of relevant adverse drug reactions is counted as one subject.

When the time to onset of adverse drug reactions cannot be calculated, it is counted as an unknown category.

For adverse events and adverse drug reactions, refer to "4.10 Adverse events and adverse drug reactions".

For the time to onset of adverse reactions, refer to "Calculate of the number of days and age" in 4.6.

The same case, the same SOC, and the same PT are processed as follows and used for tabulation.

For handling of adverse events and adverse reactions, refer to "4.10 Adverse events and adverse reactions".

Time to onset of each adverse reaction category

<PT (preferred term)>

The same case, the same SOC, and the same PT are summarized in the index case.

<SOC (System Organ Class)>

When the data are summarized according to the time of onset in the same case and in the same PT (preferred term) and the time to onset in the same case and in the same SOC (system organ class), the time to onset of adverse drug reactions is counted in each time category.

<Adverse drug reaction subjects>

The same case is counted as 1 case in the category of the time to onset of the relevant ADR in each case after being summarized in the index case.

Example :

Original data

Case No.	SOC	PT	Date of onset	Time to onset of adverse drug reactions [days]
PPD	SOC1	PT1	2017/01/01	1
	SOC1	PT1	2017/01/27	27
	SOC1	PT2	2017/01/27	27
	SOC1	PT3	2017/03/04	63

Identical subjects, identical SOC, and identical PT are summarized in the index case.

Case No.	SOC	PT	Date of onset	Time to onset of adverse drug reactions [days]
PPD	SOC1	PT1	2017/01/01	1
	SOC1	PT2	2017/01/27	27
	SOC1	PT3	2017/03/04	63

Tabulation results

Time of onset	<28	28≦～<84	84≦～<168	Unknown
SOC1	1	1	0	0
PT1	1	0	0	0
PT2	1	0	0	0
PT3		1	0	0
Subjects with adverse reactions	1	0	0	0
Cumulative incidence of adverse reactions	1	1	1	0

Total number of subjects

<PT (preferred term)>

The same case, the same SOC, and the same PT are summarized in one case regardless of the date of onset.

<SOC (System Organ Class)>

The same case and same SOC are summarized in one case regardless of the date of onset.

<Adverse drug reaction subjects>

The same case is summarized in one case regardless of the date of onset.

Categorization of days to onset of adverse drug reactions:	<28、28≦～<84、84≦～<168、168≦～<252、252≦～<365、365≦、Unknown
Definition of time to onset of adverse drug reactions:	For the calculation of the time to onset of adverse reactions See 4.6 Calculate of Days and Age. However, the date of onset of adverse reaction is defined as the date of onset.

6.3.3. Total dose until onset of adverse reaction by type (Table2.03)

Analyses included:	Safety analysis subjects
Analysis content:	The total dose category and total dose of drug will be summarized in the same manner as in "6.3.2 Time to onset of adverse drug reactions (Table2.02)". For the total dose of drug and the total dose of drug until the onset of adverse reactions, refer to "6.2.1 Patient characteristics (Table1.01)".
Total dose of drug to onset of side effects:	<100 mg, 100 mg≦～<300 mg, 300 mg≦～<600 mg, 600 mg≦～<900 mg, 900 mg≦～<1300 mg, 1300 mg≦, "unknown"

6.3.4. Incidence of reaction/event by seriousness (Table2.04～Table2.07)

Analyses included:	Safety analysis subjects
Analysis content:	For each reaction/event, the proportions by PT will be summarized by seriousness (total number/seriousness). The denominator of the ratio is the number of subjects included in the safety analysis. The output permutation is output in descending order of the number of SOC in the total number of columns, in descending order of the international consensus order of SOC, in descending order of the number of PT subjects, and in descending order of the number of PT subjects if there are no total number columns, in SOC international consensus order, and in PT coding order. In addition, the number of subjects with ADRs/AEs and the proportion of ADRs/AEs will be summarized by outcome. The denominator of the percentage will be the number of subjects included in the safety analysis. ※If the same case and the same SOC, PT are present in the summary by outcome, the following priorities will be adopted and tabulated. ①Serious > non-serious; ② Fatal > Sequelae > Unrecovered > Remitted > Recovery > Unknown

6.3.5. Adverse reaction/event status (Table2.08～Table2.11) by safety considerations.

Analyses included:	Safety analysis subjects
Analysis content:	For adverse drug reactions/events, the proportions by PT will be summarized by seriousness (total number and seriousness) for each safety specification. The output order is output in descending order of the number of SOC in the total number of columns, SOC coding order, descending order of the number of PT subjects, and PT coding order. The number of subjects with reaction/event and the proportion of subjects with reaction/event will be summarized by outcome for each safety consideration. The denominator is the number of subjects included in the safety analysis.

※If the same case and the same SOC, PT are present in the summary by outcome, the following priorities will be adopted and tabulated.

Death > Sequelae > Unresolved > Remitted > Recovery > Unknown

Table2.08.1～Table2.11.1: Hypersensitivity such as anaphylaxis

Table2.08.2～Table2.11.2: Infectious Disease

Table2.08.3～Table2.11.3: malignant tumor

6.3.6. Incidence of adverse reactions in subjects with special characteristics (Table2.12, Table2.13)

Analyses included:	Safety analysis subjects
Analysis content:	The proportions of adverse drug reactions (total/serious) by PT will be tabulated for subjects with special patient characteristics. The denominator of the ratio is the number of subjects included in the safety analysis by patient characteristics. The output order is output in descending order of the number of SOC in the total number of columns, in international consensus order of SOC, in descending order of the number of PT, and in PT coding order. In addition, the number of subjects with adverse drug reactions and the incidence of adverse drug reactions will be tabulated according to the outcome. The denominator of the percentage will be the number of subjects included in the safety analysis by patient characteristics. ※If the same case and the same SOC, PT are present in the summary by outcome, the following priorities will be adopted and tabulated. ①Serious > non-serious; ② Fatal > Sequelae > Unrecovered > Remitted > Recovery > Unknown
Special patient characteristics:	Table2.12.1, Table2.13.1: Renal dysfunction Table2.12.2, Table2.13.2: Hepatic dysfunction Table2.12.3, Table2.13.3: Pediatric Table2.12.4, Table2.13.4: Elderly Table2.12.5, Table2.13.5: Pregnant women

6.3.7. Duration of drug treatment by reason for discontinuation/completion of drug (Table2.23)

Analyses included:	Safety analysis subjects
Analysis content:	The number of subjects who discontinued or completed drug treatment and the reason for discontinuation or completion of treatment will be summarized by the duration (days) of drug treatment until discontinuation or completion. The reasons for discontinuation/completion of administration are duplicated.
Categories of drug treatment duration until discontinuation/comp	<28、28≦～<84、84≦～<168、168≦～<252、252≦～<365、Unknown

letion of treatment:

Defining the duration (days) of drug treatment until discontinuation/completion of treatment: See "Calculation of the number of days and age" in "4.6 Calculation of drug duration of administration before discontinuation/completion of administration."
However, the target date is the date of completion of drug administration.

6.4. Evaluation of effectiveness

6.4.1. Effectiveness proportion by patient characteristics (Table3.01)

Analyses included: Effectiveness analysis subjects

Analysis content: The number of subjects surveyed, effective subjects, ineffective subjects, and effective proportions with 95% confidence intervals will be calculated for each patient background item.

The active proportion is calculated using the following formula.

Effective proportion = number of effective subjects/number of investigated subjects for each background item × 100

Effectiveness is assessed as follows.

- "Effectiveness" in the [Overall Evaluation of Effectiveness] of the case report form is "effective" and "effective"
- If "Effectiveness" in the [Overall Evaluation of Effectiveness] of the case report form is "Ineffective", "Ineffective"
- When the "effectiveness" of the [Overall Effectiveness Evaluation] of the case report form has an input in "Undeterminable", it is set to "Undeterminable"
- If other than the above, indicate "unknown"

Patient characteristics items: Same section as "6.2.1 Patient characteristics (Table1.01)"

6.5. Listing

- ✧ Availability List for Review (Listing1)
- ✧ List of adverse events (Listing2)
- ✧ Case report form and List of Subjects (Lisiting3)
- ✧ List of Serious Adverse Drug Reactions (Listing5)
- ✧ List of Adverse Events by Safety Specification (All subjects) (Listing6.1)
- ✧ List of Adverse Events by Safety Specification (Serious subjects) (Listing6.2)
- ✧ Summary of fatal subjects (Listing7)
- ✧ List of adverse events in subjects excluded from safety analysis (Listing8)

- ✧ List of subjects for change in reason for use (Listing9)
- ✧ Incidence of adverse reactions/infectious diseases in the additional safety monitoring plan (Form 12)
- ✧ List of subjects surveyed (Format 16)

6.6. Exploratory analysis

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

6.7. Proprietary form

6.7.1. Summarized statistic of blood eosinophil count. (Table2.21)

Analyses included: Safety analysis subjects

Analysis content: The number of all subjects or subjects who continued for 52 weeks will be tabulated for the analysis subjects.

In addition, for the blood eosinophil count, the summary statistics will be calculated for the analysis studies according to the time of evaluation.

The above analyses will be performed in all subjects and in subjects who continue for 52 weeks.

Table2.21.1: all subjects

Table2.22.2:52 Weeks Continued

Time of evaluation: See 4.8.1 "Recruitment Data by Time of Evaluation of Blood Test Items"

6.7.2. IgE levels in subjects with and without prior omalizumab use. (Table2.22)

Analyses included: Safety analysis subjects

Analysis content: Calculate the number of subjects according to the history of omalizumab use.

We will also calculate a summary statistic for total serum IgE levels by history of omalizumab use.

Definitions : See 4.8.1 "Recruitment data of blood test items by assessment period" for collection of data on total serum IgE levels.

6.7.3. Percentage of use of oral corticosteroids for bronchial asthma (Table2.24)

Analyses included: Safety analysis subjects

Analysis content: The presence and proportion of oral corticosteroids used in prior and concomitant medications will be tabulated.

However, in the case of concomitant medications, the indication is bronchial asthma for indication.

The denominator of the proportion is the number of subjects included in the safety analysis.

Definition of oral corticosteroids: Drugs listed in "Determination of the dose of oral corticosteroids used in Appendix B and concomitant medications."

6.7.4. Asthmatic exacerbation (Table3.05)

Analyses included: Effectiveness analysis subjects

Analysis content: The summary statistics and the incidence proportion per person-year are calculated for the breakdown of the following bronchial asthma exacerbations according to the time of evaluation.

① Number of bronchial asthma exacerbations

② Bronchial asthma exacerbations requiring hospitalization (number of times)

③ Bronchial asthma exacerbations requiring emergency department (number of times)

④ Bronchial asthma exacerbations requiring systemic steroid use (number of episodes)

⑤ Bronchial asthma exacerbations requiring hospitalization (days in hospital)

<Incidence>

The incidence proportion per person-year (IR: Incidence Rate) is calculated.

IR is calculated according to the following formula.

IR per capita year = “number of times/days”/T x 1

Here, T is the total of the observation period of the subjects /364 (52 weeks are converted to 1 year).

Time of evaluation: 52 weeks prior to initiation of drug

52 weeks after initiation of drug treatment or until discontinuation

6.7.5. ACT score (Table3.07, Figure 3.07.1 (Fig. 1_Boxplot)).

Analyses included: Effectiveness analysis subjects

Analysis content: The number of all subjects or subjects who continued for 52 weeks will be tabulated for the analysis subjects.

In addition, for ACT of the studies included in the analysis, the summarized statistic will be calculated according to the assessment period, and a Boxplot will be prepared.

The above analyses will be performed in all subjects and in subjects who continue for 52 weeks.

However, the evaluation time to calculate the summary statistics is as follows for all subjects and for subjects who continue for 52 weeks.

All subjects:

- ACT scored (at the beginning of drug treatment)
- ACT scored (12 weeks after initiation of drug treatment)
- ACT scored (24 weeks after initiation of drug treatment)
- ACT scored (52 weeks after initiation of drug treatment)
- ACT scored (12 weeks after initiation of drug treatment-at the beginning of drug treatment) ≧3
- ACT scored (24 weeks after initiation of drug treatment-at the initiation of drug treatment) ≧3
- ACT scored (52 weeks after initiation of drug treatment-at the start of drug treatment) ≧3

52-week continuation case:

- ACT scored (at the beginning of drug treatment)
- ACT scored (12 weeks after initiation of drug treatment)
- ACT scored (24 weeks after initiation of drug treatment)
- ACT scored (52 weeks after initiation of drug treatment)
- ACT scored (12 weeks after initiation of drug treatment-at the beginning of drug treatment) ≧3
- ACT scored (24 weeks after initiation of drug treatment-at the initiation of drug treatment) ≧3
- ACT scored (52 weeks after initiation of drug treatment-at the start of drug treatment) ≧3

Table3.07.1, Figure3.07.1: all subjects

Table3.07.2, Figure3.07.2: 52 Weeks Continued

6.7.6. Respiratory function tests (Table3.08)

Analyses included: Effectiveness analysis subjects

Analysis content: Calculate respiratory function test values (PEF) and calculate the proportion of the corresponding number of subjects by assessment period for the analysis subjects.

The denominator of the ratio is the number of subjects for analysis.

In addition, summary statistics of respiratory function test values will be calculated by assessment period. The 25% and 75% points of the summary statistics are not calculated.

6.7.7. The three items defined as clinically remission (Table3.09)

Analyses included: Effectiveness analysis subjects

Analysis content: The number of subjects who met the following conditions and the number of subjects who did not meet the following conditions for subjects who continued for 52 weeks will be tabulated for the analysis subjects.

① Subjects who did not experience exacerbation after treatment among those who had progression events prior to drug treatment

② Subjects who did not require oral corticosteroids to treat bronchial asthma prior to drug administration after administration.

③ Among subjects with ACT scores before and after drug treatment, those with ACT scores of 20 points or more after treatment were 23 points

④ ①~ Subjects meeting all of the conditions in ③ (only relevant subjects were tabulated)

7. ChangeLog

Date	Version	Author	Description
16-Mar-2018	1.0	PPD	First edition
20-Aug-2018	2.0	PPD	The following items were modified according to the standard analysis plan: ・2.2 Dictionary to be used: The description of the lexicon name of the disease name was modified in the description to be decided after the study by the team. ・4.2 Analysis set and sites: Representation of the definitions of contract sites, enrollment sites, enrollment subjects, safety analysis sites, safety analysis subjects, effectiveness analysis subjects, asthma exacerbation analysis subjects, respiratory function test analysis subjects, and ACT analysis subjects were modified. ・4.9.2 Subjects continued for 52 weeks, subjects discontinued/completed: Added definition. ・4.11.1 Definition of adverse events/adverse drug reactions: The expression of the definitions of adverse events and serious adverse drug events (serious adverse drug reactions) was modified. ・4.15.2.3 The inclusion data for the assessment period of the Asthma Control Test (ACT) were added to the specification for the absence of data entry in "Discontinuation/End of Treatment". ・5.4.4 The indicated digits of the statistic: ①Proportions, proportions: The number of indicated digits was modified from decimal 2 to 1. ②p-value: The contents without "*" were corrected. ・5.5 Sample code: Wilcoxon signed rank test with additional sample codes for estimation of confidence intervals of means. ・6. Main analysis items: ①It was decided to output forms other than villa 1 and villa 11. ②Appendix 2: The title of "Case composition" was changed, and "Site" or "Number" was deleted from the display items. The form number was changed to Figure 1. ③Appendix 3: The title was changed to "Case composition ratio". And, the investigation form fixation case was removed from the analysis object. ④Appendix 4: The title was changed to "List of Incidence of Adverse Drug Reactions by Patient Background". The number of subjects with adverse drug reactions (%) was modified to the proportion of adverse drug reactions. ⑤Appendix 5, Appendix 6, Appendix 7, and Appendix 8: Percentages were standardized. ⑥Appendix 10: The title was revised to "Time to onset by type of adverse reaction." In addition, the tabulation of the number of subjects was deleted. ⑦Specifications for the following forms were added:

Date	Version	Author	Description
			-Appendix 13 -Appendix 14 -Appendix 15 -Appendix 16
20-Feb-2019	3.0	PPD	Changes in chapter composition were made in line with the updated standard analysis plan. 3. The following definitions were added or modified by terminology: ・Modification of the Definition of "Date of Completion of drug Administration" ・Addition of definition of last observation day 4.2. Modification of the definition of exclusion conditions was performed in the analysis set and institutions. 4.7. In the calculation of days and age, the following definitions were added or deleted: ・Deletion of "Total number of days administered" ・Addition of the definition of "total observation period" 6.3.2. The following specifications were modified in the time to onset of adverse drug reactions: ・Total number of days administered was changed to the total observation period. The following specifications for the sort order of forms were changed. ・6.6.4. Number of subjects according to complication symptoms ・6.6.5. Number of subjects by prior drug Changes to the analysis set and modifications to the analysis content were performed in the following specification of each form: ・6.7.1. Exacerbation of asthma (number of asthma episodes) ・6.7.2. Asthma exacerbations (days in hospital) ・6.7.3.ACT score ・6.7.4. Respiratory function test values Specifications for the following items were added as a unique form. ・6.3.3 Total dose until onset of adverse reaction by type ・6.7.5. Summary statistics of blood eosinophil count ・6.7.6. IgE levels in subjects with and without prior omalizumab use.
18-Sep-2019	4.0	PPD	In order to ensure consistency with the standard analysis plans and EGPA surveys for the Seventh Periodic Safety Report, and to make more appropriate expressions, the tabulation classification was reviewed as described below, and the target population was changed. 4.8.1. In the inclusion data for each time point for haematology parameters, it was added that subjects who discontinued the study should be enrolled in the imputation condition "Week 52 after the initiation of drug treatment or at the time of discontinuation/completion." In addition, the definition of "52 weeks after the initiation of drug treatment or at the time

Date	Version	Author	Description
			of discontinuation/completion" was modified for the inclusion of haematology parameters by assessment period. 4.8.2. In the inclusion data for each time point for the effectiveness endpoint, it was added that subjects who discontinued the study should be enrolled in "Week 52 after the initiation of drug treatment or at the time of discontinuation/completion." In addition, Adoption data by time point for effectiveness endpoints: "Discontinuation/End of Treatment" was modified from "Adoption data for Asthma Control Test (ACT)" 6.2.1. Patient characteristics (Table1.01): Additional definition total days of treatment 6.3.2. Time to onset of adverse drug reactions (Table2.02): Modification of classification 6.6.5. Number of subjects (Table2.18) by drug prior to treatment: Deletion of the following items • Number of investigated subjects used for calculation • Mean daily dose 6.7.1. Summary statistic for blood eosinophil count (Table2.21): Change in analysis set 6.7.3. Asthma exacerbations (number of asthma episodes) (Table3.05): Changes in the specification of the analysis set 6.7.4. Asthmatic exacerbations (days in hospital) (Table3.06): Change in specification of the analysis set 6.7.5. ACT Score (Table3.07): Change in analysis set 6.7.6. Respiratory function tests (Table3.08): Change in analysis set and modification of analysis text
13-Mar-2020	5.0	PPD	The following specifications were modified to ensure consistency with the standard analysis plan and to make the expressions more appropriate. 4.3.1. Subjects excluded from safety analysis: Modified definitions outside the contract period 4.11. Safety Specification, Definition of Complications: Added "Definition of Complications" to the item name. 6.1.1. Case Composition (Figure1.01): Additional Aggregation of Institutions 6.3.2. Time to onset of adverse drug reactions (Table2.02): Additional time to onset of adverse drug reactions 6.3.7. Duration of drug treatment by reason for discontinuation of drug (Table2.23): Additional specification of the new form 6.6.5. Number of subjects (Table2.18) by prior medication: "Product name" was revised to "drug name"
11-Sep-2020	6.0	PPD	The following specifications were modified to ensure consistency with the standard analysis plan and to investigate the effectiveness. 6.1.1. Case composition (Figure1.01): Additional specification of case composition

Date	Version	Author	Description
			on the follow-up form Specifications for the following items were added as a unique form. 6.7.3. Percentage of oral corticosteroids used (Table2.24): Adding the specification of a new form 6.7.4. Daily dose of oral corticosteroids (Table2.25): Additional specification of the new form
22-Apr-2021	7.0	PPD	4.7 Calculate of days and age: "Duration of treatment (days) added to the definition of period) 6.2.1 Patient characteristics (Table1.01): The total number of days of administration [days] was deleted because it was equivalent to the total number of doses [times], the number of days of administration [days] was added, and the total observation period [days] was added.
31-May-2022	8.0	PPD	4.1 Number of subjects with adverse events (adverse drug reactions): Additional handling of adverse events during the observation period 4.2 Analysis set/site: Subjects included in the follow-up analysis and subjects included in ACT analysis were added. 4.7 Calculation of days and age: The calculation formula was added to the definition column for the time to onset of adverse drug reactions, and the term "total observation period" was changed to the observation period. 6.2.1 Patient characteristics: The blood eosinophil count category was changed according to the package insert category, and Table1.01.6 (the effectiveness proportion in subjects who discontinued treatment or had completed the reason) was added. 6.3.5 Adverse reaction/event status by safety considerations: The text was interrupted, so it was added. 6.7.4 Daily dose of oral corticosteroids with additional definition of mean dose The following forms were added to check OCS use before and after drug administration Use of Pretreatment and Concomitant Medications (OCS) for Table2.26 Bronchial Asthma. 6.7.8 Added ACT Score: Boxplot and Bar Graph Creation. Additional number of subjects items with a score-difference of 3 or more before and after drug administration were added.
02-Sep-2022	9.0	PPD	4.1 Number of subjects with adverse events (adverse drug reactions): Additional reference for definition of observation period 4.2 Analysis set/site: Additional asthma exacerbation analysis set 4.5 Date of completion of administration at the time of continuation of administration: Modified formula for calculation of date of completion of administration 4.7 Calculation of days and age: Deletion of description for 1 year 4.12 Addition of handling of continuation/discontinuation/completion of administration, deletion of existing descriptions due to changes in handling

Date	Version	Author	Description
			5.4 Test: To confirm the signal of influential factors rather than the significance test, the name and content of the title are adjusted to the standard. 6.6.7 Incidence of ADRs in items with significant differences: To confirm the signal of influential factors rather than the significance test, the name and description are adjusted to the standard. 6.7.3 Percentage of use of oral corticosteroids: The word "for bronchial asthma" was added at the head of the item name, and the handling of the totaling study in the combined use medicine was added to the analysis content. 6.7.4 Daily dose of oral corticosteroids: Since calculation of the mean dose was a definition that cannot be handled by data collected on the case report form, it was deleted 6.7.6 Exacerbation of asthma (number of asthma): the number of asthma exacerbations was added because three categories were established
21-Sep-2023	10.0	PPD	Change signer based on amendment of procedure manual 3. Defining the terms: "date of last dose of drug" is set as "date of completion of drug administration" and improved. Last observation day was deleted because it was used as the "End of observation day (week 52)" 4.5. Date of completion of administration at the time of continuation of administration: 4.11. Deletion of this item to use handling of continuation of administration/discontinuation of administration/completion 4.5. Handling of presence/absence: Additional 4.6. Number of days: Calculation of age. "Observation period of drug" was changed to "administration period of drug" 4.11. Handling of continuation/discontinuation/completion of administration: The term "drug treatment observation date" was changed to "observation date (52 weeks)". The calculation formula was partially modified in order to revise the calculation method for the observation date (week 52). Addition of the definition of "the follow-up date" 4.12. Handling of subjects with a change in administration purpose: 6.2.1. Patient characteristics: "Age 3 (years)" was added to Table1.01.1 for EMA Article46 response. Table1.01.6 Delete 6.3.1. List of adverse reactions by patient characteristics: Added 95% confidence interval output for the incidence proportion of adverse reactions based on the protocol 6.4.1. Effective proportion by patient background: The 95% confidence interval output of the effective proportion was added based on the description in the protocol. 6.5. List: Added Listing9 (list of subjects for identification of subjects with change in reason for use) 6.6.1. Correlation of factors: Review of exploratory variables, deletion of "Age 2 (years),""

Date	Version	Author	Description
			"Reason for drug use," addition of "Smoking history" and "Blood eosinophil count (at the start of drug administration)" 6.7.5. Use of pre-treatment and concomitant medication for bronchial asthma: Results of reconsideration not required and deleted 6.7.4. Exacerbation of asthma: change from exacerbation of asthma (number of asthma) to exacerbation of asthma. The content of the analysis was modified or changed with reference to the specification of EGPA survey. "Exacerbation of asthma (number of days in hospital)" was also tabulated in this section. 6.7.7 Three items defined as clinical remission were added to the secondary study of clinical remission.

Appendix A : How to identify Appendix A adverse events

Adverse events used in the analysis of this survey will be identified as follows:

◆ Prerequisite

Assessment of malignancy will be performed by SMQ coding as described in "4.11 Definitions of Safety/Complications" in SAP.

Adverse events other than malignancy occurring during follow-up will not be included in the analysis.

◆ Adverse events to be assessed

The following adverse events occur.

- Adverse events occurring by the end day of observation (Week 52)
- Adverse events occurring during follow-up (malignancy only)

Dates of onset of adverse events	※1 of the end-of-observation date (52 weeks)	Tracking Starting Date ※1	Follow-up Ending Date ※1	Judgement		
				Conditions	Subjects	
					Other than malignancy	Malignant tumor
Yes ※2	Yes	-	-	<= Day of onset, end of observation (Week 52)	Applicable	Applicable
		Yes	Yes	Start date of follow-up <= onset date <= end date of follow-up	Not applicable	Applicable
	Unknown	-	-	All relevant events are included in the analysis	Applicable	Applicable
Unknown	-	-	-	All relevant events are included in the analysis	Applicable	Applicable

※1. See "Handling of Continuation/Discontinuation/Completion of Treatment" in 4.11"

※2. If only "Day" is unknown, judge using the following procedure

However, when the year or month is unknown, the date is treated as "unknown"

① Extract the date and month of the decision condition

② Compare the date and month of each decision condition to determine whether the decision condition is met

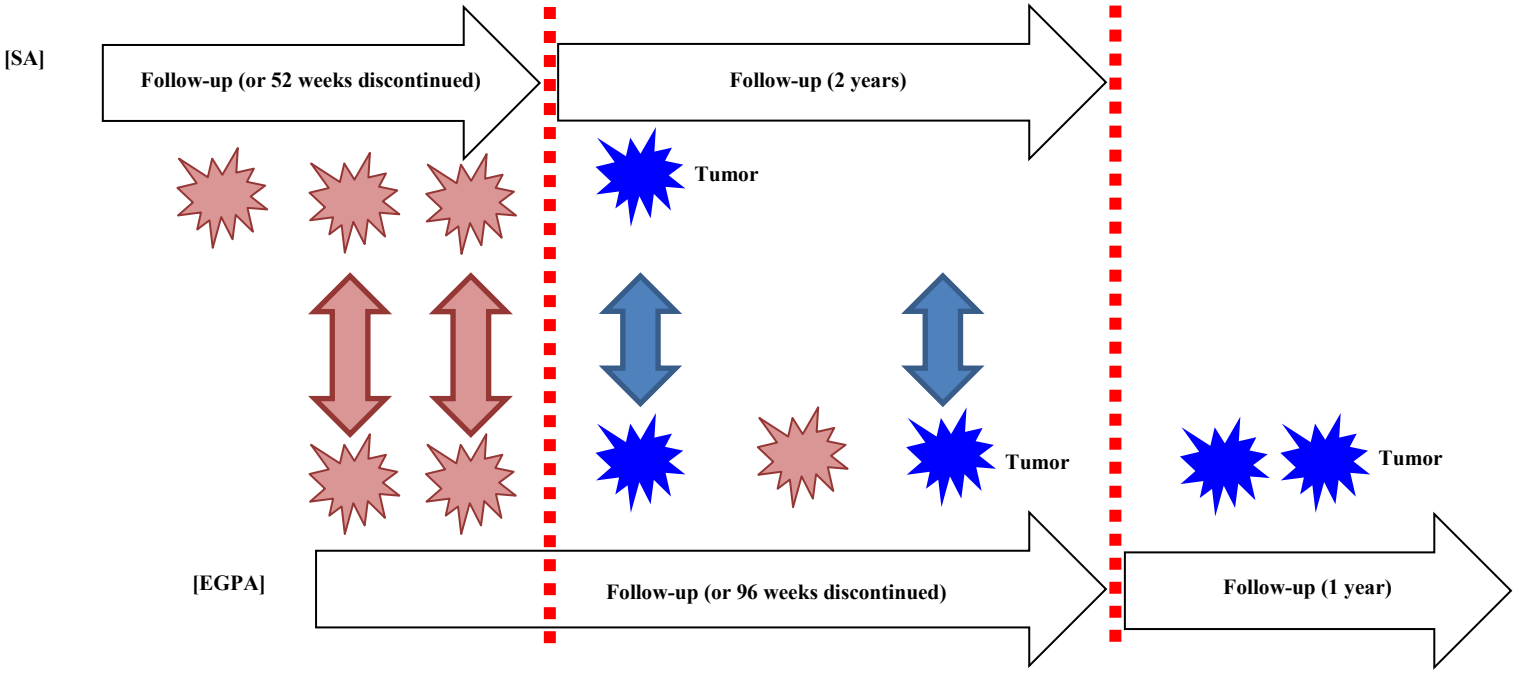
e.g., date of onset of adverse event, 2018/08; last observation day, 2018/11/20

① Day of onset of adverse event: 2018/08, last observation day: 2018/11

② Day of onset of adverse event (2018/08) < = last observation day (2018/11)

These adverse events will be included in the analysis.

Reference: Determination of adverse events of severe asthma (SA) and eosinophilic polyangiitis granulomatosis (EGPA)



Appendix B : How to determine the dose of oral corticosteroids used in Appendix B treatment and concomitant medications

Transform the unit of dose of oral corticosteroids as shown in the table below

List of unit transformations

Classification of oral corticosteroids used in prior and concomitant medications	Units
Oral steroids	Mg

*:Convert to prednisolone equivalent

List of coefficients of prednisolone equivalent

After converting to "μg" in units, calculate the dose by multiplying by the following factors.

Generic name	Drug code (7 digits)	Product name	Clinical dose	Coefficient
Hydrocortisone	2452002	Cotolyl	20	0.250
Hydrocortisone Succinate	2452400		20	0.250
Cortisone Acetate	2452001	Corton	25	0.200
Prednisone		Unmarketed	5	1.000
Prednisolone	2456002	Predonine	5	1.000
Prednisolone succinate	2456406		5	1.000
Methylprednisolone	2456003	Medrol	4	1.250
Methylprednisolone Succinate	2456400		4	1.250
Triamcinolone	2454003	Redacoat	4	1.250
Triamcinolone acetonide	2454402		4	1.250
Dexamethasone	2454002	Decadron	0.75	6.667
Dexamethasone phosphate	2454405		0.75	6.667
Parametasone acetate	2454001	Parametasone	2	2.500
Betamethasone	2454004	Rinderon	0.75	6.667
Betamethasone phosphate	2454005		0.75	6.667