NOVARTIS

Clinical Development

CIGE025/Omalizumab

CIGE025F1301 / NCT03369704

A 12 week, multi-center, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of omalizumab in adult and adolescent patients with inadequately controlled severe Japanese cedar pollinosis despite the current recommended therapies

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
11-Dec-2017	Prior to FPFV		Final 2.0	
19-Jul-2018	Prior to DB lock	Creation of Amendment 1	- Modified the member of Author. (Author members are changed.)	Cover
			- Objectives and related endpoints Study objectives and endpoints Added the footnote about the definition of symptom free days.	1.2
			- Severe symptom period Clalified that the severe symptom period will be set as a period not exceeding April 13. - Baseline Added handle of unscheduled visits. - Handling of data from premature discontinuation or unscheduled visit Added the details of data handling. - Handling of duplicatedata in patient-reported outcomes (PRO) New addition. - Definition of evaluation visit Added the details of data handling.	2.1.1
			- Subgroup of interest Deleted the following subgroups; Age (<15 years/ >=15 years, and Having cedar pollinosis symptoms at the initial drug administration (Yes/ No). Modified the subgroup categoty of Total IgE concentration at baseline and Severity of cedar pollinosis in 2017.	2.2.1
			- Demographic characteristics Deleted the following items; Age category; <15 years/ >=15 years. - Disease characteristics	2.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Deleted the following items; Coexistence of perennial allergic rhinitis; Nasal eosinophil count; Not done. Modified the following item; Japanese cedar pollinosis related medical history; Severity of nasal symptom in the previous season (2017) . Deleted the category label of "Randomization strata". - Medical history Deleted the medical history from summarized items.	
			- The disposition table Clarified the analysis set of each summary.	2.3.1
			- Prior and concomitant therapies Modified the description regarding coding procedure and analysis procedure for Medication, therapies, and surgical and medical procedures.	2.4.2
			- Statistical hypothesis, model, and method of analysis Added the considering a weight of the strata for least-square mean. Clalified the data source of stratifications for the randomization.	2.5.2
			- Subgroup analyses Added details of handling of subgroup variale. - Supportive analysis using the adjusted nasal congestion score (AdNCS) Modified the description regarding definition of AdNCS, added the reference information.	2.5.4
			- The variables regarding each mean score of the symptoms and/or rescue medication Added the considering a weight of the strata for least-square mean. Added the description of Mean score for severity of sneezing, rhinorrhea and nasal	2.7.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			congestion, and Mean score for severity of itchy and watery eye. - The variables regarding symptom free days and/or rescue medication Modified the description about eatimate of stratified Hodges-Lehmann estimates. - A proportion of patients Modified the description regarding a proportion of patients with categorical mean scores. Modified the items presented as histogram. - The JRQLQ, No1 score at evaluation visit Modified the details of figures box-plot to bar graph.	
			- Adverse events (AEs) Added the summary by presenting SMQ. Modified the threashold of AEs 3% to 2%. Deleted the some of safety analyses; *Number (%) of patients reporting AEs suspected to be related to study drug by SOC, PT and maximum severity. *Number (%) of patients reporting SAEs by SOC, PT and maximum severity. *Number (%) of patients reporting SAEs suspected to be related to study drug by SOC and PT. *Number (%) of patients reporting AEs leading to discontinuation regardless of study drug relationship by SOC, PT and maximum severity . *Number (%) of patients reporting AEs leading to discontinuation related to study drug by SOC and PT. Added the some of safety analyses; *Number (%) of patients reporting AEs by SMQ. *Number (%) of patients reporting AEs by SMQ and PT.	2.8.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			- Adverse events of special interest / grouping of AEs Deleted the following analyses; Laboratory triggers. Clalified the summary for the AEs of special interest.	2.8.1.1
			- Laboratory data Deleted the following analyses for laboratory data; Frequency table by visit. (Urinalysis), Boxplot by visit. (Hematology, Biochemistry). Added the following analysis for laboratory data; Descriptive summary statistics for post-baseline maximum values and their changes from baseline in liver parameters. Modified the criterion for the notable abnormalities of platelets.	2.8.3
			- PK/PD analyses Modified the description about %changes from baseline to each visit. Added description; Both of Serum total IgE [IU/mL] and free IgE [ng/mL] will be presented in the same unit [ng/mL].	2.10
			- e-Diary assessment (Nasal symptoms, Ocular symptoms, Medication use, and Impairment of daily activities) Added the explanation about e-Diary data collection and added handling of collection date.	2.11.1
			- Computation rule for Variables Modified the description "rescue drug use" to "comcomitant/ rescue drug use".	2.11.1.5
			- Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ) Added the analysis of total scores of JRQLQ II.	2.11.2
			[redacted]	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			[redacted]	
			- Change to protocol specified analyses Added changes described in the following sections; Section 2.5.2, 2.7.2, 2.8.1	4
			- Rule of exclusion criteria of analysis sets Modified the No. of reference tables Table 1 to Table 5-1, and Table 2 to Table 5-2.	5.4
			- Reference Added the reference regaring AdNCS.	6
			Minor update for grammatical error and typo. - Subgroup of interest (2.2.1) - Patient disposition, demographics and other baseline characteristics (2.3) - Statistical hypothesis, model, and method of analysis (2.7.2) - Adverse events of special interest / grouping of AEs (2.8.1.1) - Laboratory data (2.8.3) [redacted]	2.2.1 2.3 2.7.2 2.8.1.1 2.8.3 2.13

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List of abbreviations

AdNCS	Adjusted Nasal Congestion Score
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
CSR	Clinical Study Report
DBL	Database Lock
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FPFV	First Patient First Visit
IgE	Immunoglobulin E
IRT	Interactive Response Technology
JRQLQ	Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ No.1)
LPLV	Last Patient Last Visit
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCS	Nasal Congestion Score
PD	Pharmacodynamics
PD	Protocol Deviation
PK	Pharmacokinetics, Pharmacokinetic set
PRO	Patient-Reported Outcomes
PT	Preferred Term
QOL	Quality of Life
RAN	Randomized set
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SI	International System of Units
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TFL	Tables, Figures, Listings
ULN	Greater than Upper Limit of Normal range
[redacted]	[redacted]

1 Introduction

This Statistical Analysis Plan (SAP) describes the planned statistical methods for CIGE025F 1301 study. It is planned as

- A draft of Section 9.7 (Statistical methods planned in the protocol and determination of sample size) of the clinical study report (CSR)
- A draft of Appendix 16.1.9 (Documentation of statistical methods) of the CSR

Appendix 16.1.9 text will contain details of statistical methods and issues that are too long to be included in the CSR text (Appendix 16.1.9 is not mandatory for abbreviated and synoptic reports.).

The statistical methods planned in this document will also be used for Benefit & Risk assessment of the study drug.

It is written in future tense. It will be reviewed and updated (including conversion to past tense) for entry into the CSR after the analysis has taken place.

1.1 Study design

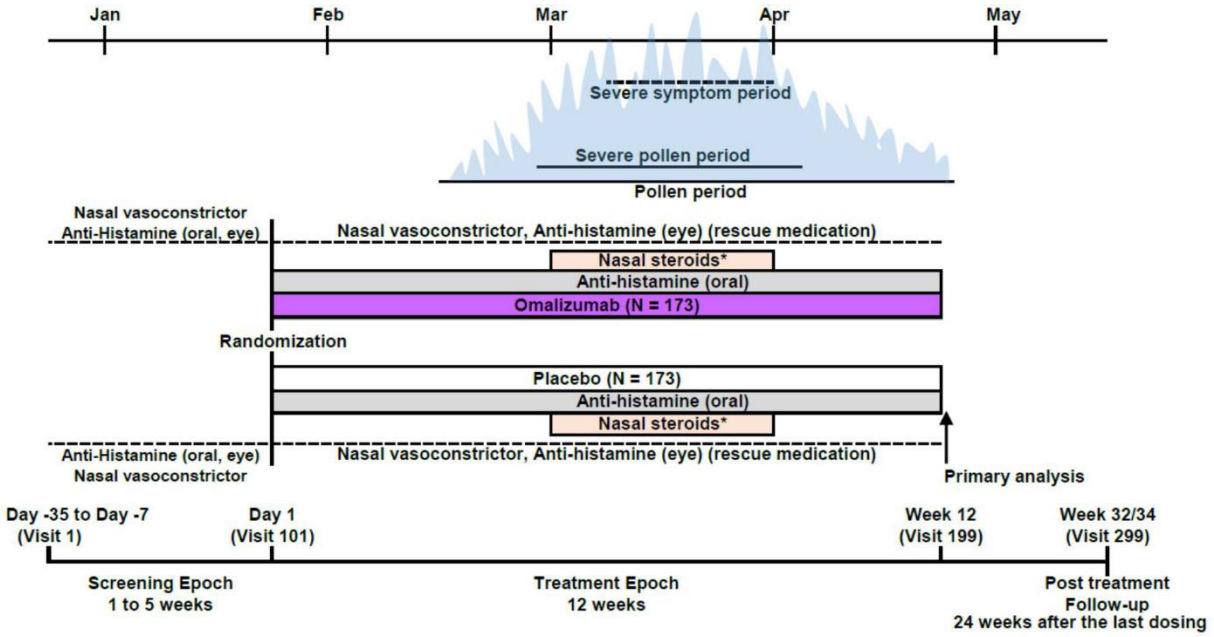
CIGE025F1301 is a Phase III multi-center, randomized, double-blind, placebo-controlled study in patients with severe Japanese cedar pollinosis, whose symptoms were inadequately controlled despite the current recommended therapies (nasal corticosteroid plus one or more medications out of anti-histamine (second generation), leukotriene receptor antagonist, or prostaglandin D2/thromboxane A2 receptor antagonist) in the previous 2 Japanese cedar pollen seasons. The purpose of this study is to demonstrate the efficacy and safety of omalizumab compared with placebo, on top of SoC (anti-histamine and nasal corticosteroid).

Approximately 346 patients will be enrolled in the Kanto-area of Japan.

Eligible patients will be randomly assigned in a 1:1 ratio to receive omalizumab or placebo by subcutaneous injection. Patients will be stratified using Interactive Response Technology (IRT), based on the age group (≥ 12 to < 15 years and ≥ 15 to < 75 years), coexistence of perennial allergic rhinitis (Yes / No), dose frequency (every 2 weeks and 4 weeks) and having cedar pollinosis symptoms at the time of initial drug administration (Yes / No).

The study consists of 3 distinct study epochs:

- Screening epoch: Day -35 to Day -1 (1 - 5 weeks)
- Treatment epoch: Day 1 to Day 85 (12 weeks)
- Post-treatment follow-up: Day 225/239 (24 weeks after the last dosing)



*Start date of fluticasone propionate use and duration of fluticasone propionate use (2 - 4 weeks) will be determined by the sponsor based on the forecast of cedar pollen scattering.

There will be no interim analysis in this study. A primary analysis will be performed on all the data during the screening epoch and the treatment epoch after all patients complete the treatment epoch to support the registration. The database lock (DBL) for this analysis will occur when all the patients complete 30 days safety evaluation following the end of the treatment epoch or prematurely discontinue the study. After completion of post-treatment follow-up visit for all patients, PK analysis and anti-omalizumab antibody analysis for the follow-up epoch will be performed separately.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • To demonstrate the efficacy of omalizumab compared with placebo	**Endpoint(s) for primary objective(s)** • Mean nasal symptom score during the severe symptom period
Secondary Objective(s) • To evaluate the efficacy (symptoms, quality of life impairment) of omalizumab compared with placebo	**Endpoint(s) for secondary objective(s)** • Mean score of the following endpoints during the severe symptom period - Ocular symptom score and nasal ocular symptom score - Nasal symptom medication score, ocular symptom medication score, and nasal ocular symptom medication score

Objective(s)	Endpoint(s)
	- Score for severity of sneezing, rhinorrhea and nasal congestion - Score for severity of itchy and watery eye - Score for impairment of daily activities • Symptom free days (days with all nasal symptoms are not more than mild[a] in severity) during the severe symptom period • Use of rescue medication (tramazoline hydrochloride, levocabastine hydrochloride) during the severe symptom period - Rescue medication score - Number of days with no rescue medication - Amount of rescue medication used • Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ, No1) score at evaluation visit
• To evaluate the safety of omalizumab compared with placebo	• Adverse events, serious adverse events, adverse events of special interest, physical examinations, laboratory assessments, vital signs and anti-omalizumab antibodies
• To evaluate the PK/PD of omalizumab	• Serum omalizumab concentration, free IgE concentration and total IgE concentration at evaluation visit
[redacted]	

Objective(s)	Endpoint(s)
[redacted]	

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis and [redacted] according to the data analysis Section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following Sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR. All data analyses will be performed using SAS® statistical software (Version 9.4) unless otherwise noted.

The primary analysis will be conducted on all subject data at the time the treatment epoch ends or premature discontinuation. The PK analysis and anti-omalizmab antibody analysis for the follow-up epoch will be conducted on all subject data at the time the post-treatment follow-up epoch ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

2.1.1 General definitions

Severe symptom period: The three weeks where the cumulative value of the mean daily nasal symptom score is the maximum. The severe symptom period will be set as a period not exceeding April 13. It will be specified during blinded review before DBL and will be the same for all patients.

To specify the three week severe symptom period, the mean daily nasal symptom score will be derived as: the total nasal symptom score of all patients divided by the non-missing number of patients per day.

The three weeks must also meet one of the following criteria;

- $\geq$ 70% of the period with concomitant use of fluticasone propionate (nasal) is included in this three weeks.
- $\geq$ 70% of this three weeks includes the period with concomitant use of fluticasone propionate (nasal).

If not, severe symptom period will be extended at a minimum to meet one of the criteria above.

Severe pollen period: The period between the first and last days when ≥ 50 grains/cm2 of Japanese cedar pollen are counted. It will be announced before DBL by the sponsor based on the data of Japanese cedar pollen count.

Pollen period: The start day of the pollen period is defined as the first of 2 consecutive days when ≥ 1 grain/cm2 of Japanese cedar pollen is counted; the end day of the pollen period is the first of 3 consecutive days when no grain is counted. It will be announced before DBL by the sponsor based on the data of Japanese cedar pollen count.

Japanese cedar pollen count: The data at Chiyoda-Ku, Tokyo, which will be provided from [redacted], will be used in the study.

General descriptive statistical rules to summarize quantitative or qualitative parameters: Continuous variables will be summarized using descriptive statistics (number of non-missing data, mean, median, standard deviation, first and third quartiles, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category including a category for missing data if any.

Study day: Study day is defined as the number of days since the date of first dose of study medication. The date of first dose of study medication is defined as Day 1 and the day before the first dose of study medication is defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

- For dates on or after the first dose of study medication,
  Study day = Assessment date – Date of first dose of study medication + 1;
- For dates prior to the first dose of study medication,
  Study day = Assessment date – Date of first dose of study medication.

Baseline: In general, the last measurement (including unscheduled visits) before or at the randomization visit. For diary data, baseline is defined as an average during 7 days prior to Visit 101 (randomization).

Change from baseline: When change from baseline is of interest, the following formula will be used for each scheduled visit where baseline and post-baseline values are both available: Change from baseline = post-baseline value – baseline value.

Handling of data from premature discontinuation or unscheduled visit:

For patients who do not complete the study, the treatment/study discontinuation visit will be remapped to the next scheduled visit with reference to the planned duration between the two visits, or mapped as an unscheduled visit. If the discontinuation visit is greater or equal to half of the visit interval from the preceding scheduled visit but not exceeding the target date +7 days (the time window as allowed in the study protocol) then the discontinuation visit number will be assigned to the next scheduled visit; else it will be mapped as unscheduled visit. The data from the unmapped treatment/study discontinuation or unscheduled visit will not be used for the efficacy or by-visit safety analyses except for baseline but will be used for the summary of notable abnormalities for laboratory tests and shift tables. Data from unscheduled visits or the unmapped premature treatment/study discontinuation visits will be included in listings.

Handling of duplicatedata in patient-reported outcomes (PRO):

PRO records are entered by subjects and there is case when more than one values are entered by subject for one entry due to technical reasons. In such a case, value of the available first entry will be used.

Definition of evaluation visit:
For JRQLQ, [redacted], evaluation visit will be defined as the visit during the severe symptom period if there is a single visit during the period, and will be defined as Visit 105 or, in case Visit 105 is outside the period, the visit during the period which is the closest to Visit 105 if there is more than one visit during the period for each patient. The evaluation visit will be derived independently for each evaluation item described above. If there will be no visit during the period, the evaluation visit will be set as missing.

Classification of symptom severity and disease types of Japanese cedar pollinosis: Symptom severity and disease types will be determined according to Table 2-1 which is based on the Nasal symptom score shown in Section 2.11.1.1.

Table 2-1 Symptom severity and disease types

		Paroxysmal sneezing or Rhinorrhea *				
		4	3	2	1	0
Nasal congestion	4	Most severe	Most severe	Most severe	Most severe	Most severe
	3	Most severe	Severe	Severe	Severe	Severe
	2	Most severe	Severe	Moderate	Moderate	Moderate
	1	Most severe	Severe	Moderate	Mild	Mild
	0	Most severe	Severe	Moderate	Mild	No symptom

*Select more severe one, sneezing or rhinorrhea

Disease type: Sneezing and rhinorrhea type; white cells, Nasal blockage type; light gray cells, Combined type; dark cells

2.2 Analysis sets

Randomized set (RAN): The RAN will include all randomized patients, regardless of whether they received any study medication. Patients in the RAN will be analyzed according to the treatment assigned at randomization. Patients who are randomized in error will be excluded from the RAN.

Full analysis set (FAS): The FAS will consist of all patients in the RAN who received at least one dose of study medication. Following the intent-to-treat principle, patients in the FAS will be analyzed according to the treatment they are assigned to at randomization.

Safety set (SAF): The SAF will consist of all patients who received at least one dose of study medication. Patients in the SAF will be analyzed according to treatment actually received.

Pharmacokinetic set (PK): The PK will consist of all randomized patients who received at least one dose of study medication and have at least one evaluable PK measurement. Patients in the PK will be analyzed according to the treatment they actually received.

Note that the set of patients included in the FAS and SAF are the same except that the SAF allows the inclusion of non-randomized patients who received study medication in error. The analysis of the primary objective will be performed on the FAS. The FAS will also be used for the analysis of all other efficacy endpoints. The SAF will be used for the analysis of all safety endpoints. The PK will be used for PK analysis.

2.2.1 Subgroup of interest

For safety analysis;

- Age (<15 years/ 15<=, <65 years/ >=65 years)
  - Age (<18 years/ >=18 years)
  - Sex
  - Dose frequency (2 weeks/ 4weeks)

For efficacy analysis;

- Age (<15 years/ 15<=, <65 years/ >=65 years)
- Age (<18 years/ >=18 years)
- Sex
- Dose frequency (2 weeks/ 4weeks).
- Coexistence of perennial allergic rhinitis (Yes/ No)
- Score of serum cedar pollen-specific IgE level at baseline (score=3/4/5,6)
- Total IgE concentration at baseline (in quartile)
- Severity of cedar pollinosis in 2017 (Most severe/ Severe/ Moderate)
- Type of cedar pollinosis in 2017 (Sneezing and rhinorrhea type/ Nasal blockage type/ Combined type)

Refer to Section 2.5 and 2.8 in this document for subgroup analyses.

2.3 Patient disposition, demographics and other baseline characteristics

Demographics, disease characteristics, key efficacy variables and medical history at baseline will be summarized for the RAN unless otherwise specified, by treatment group that patients are assigned to at randomization using descriptive statistics (number of non-missing data, mean, standard deviation, median, first and third quartiles, minimum, and maximum) for continuous variables and number and percentage of patients in each category including a category for missing data if any for categorical variables. Unless otherwise stated, listings will be on all subjects included in the population under consideration.

No imputation will be done for missing data. No statistical analysis will be provided for baseline comparability between the treatment groups.

The summaries include

Demographic characteristics:

Variables	Category
Age (years)	(descriptive statistics)

Height (cm) Weight (kg) Body mass index (BMI) (kg/m^2)	
Age (years)	< 18 year/ >= 18 years
	<15 years/ 15<=, <65 years/ >= 65 years
Sex	Male/ Female
Race	(if applicable)
Ethnicity	(if applicable)

Disease characteristics:

Variables	**Category**
Japanese cedar pollinosis related medical history (ongoing at screening visit);	
Japanese cypress pollinosis Seasonal allergic rhinitis caused by other than Japanese cedar/cypress Perennial allergic rhinitis Chronic rhinosinusitis Allergic conjunctivitis Asthma Atopic dermatitis Urticaria Food allergy Oral allergy syndrome	Yes/ No
Japanese cedar pollinosis disease background;	
Duration of Japanese cedar pollinosis (years) Symptom score in the previous season (2017) - Nasal symptoms - Ocular symptoms	(descriptive statistics)
Symptom score in the previous season (2017) - Nasal symptoms (Paroxysmal sneezing, Rhinorrhea, Nasal congestion) - Ocular symptoms (Itchy eye, Watery eye)	0/ 1/ 2/ 3/ 4
Medication use for Japanese cedar pollinosis in the past 2 seasons - Each drug in 2016 - Each drug in 2017	Yes/ No
Severity of nasal symptom in the previous season (2017)	Most severe/ Severe/ Moderate
Type of disease in the previous season (2017)	Sneezing and rhinorrhea type/ Nasal blockage type/ Combined type
Having cedar pollinosis symptoms at the initial drug administration	Yes/ No

Symptom score at baseline;	
Mean scores of each symptom during 7 days prior to the randomization - Nasal symptoms - Ocular symptoms	(descriptive statistics)
Medication use at baseline;	
Medication use during 7 days prior to the randomization	Yes/ No
Symptom related assessment at baseline;	
JRQLQ for three part and six domains [redacted] Total IgE concentration Cedar pollen-specific IgE concentration [redacted]	(descriptive statistics)
[redacted]	[redacted]
Score of cedar pollen-specific IgE level	3/ 4/ 5/ 6

Medical history:

Medical history and current medical conditions not related to Japanese cedar pollinosis, entered on the Medical history eCRF page, will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) dictionary (the latest version). Japanese cedar pollinosis non-related current medical conditions will be summarized by primary system organ class (SOC), preferred term (PT), and treatment.

Randomized allocation to treatment:
Randomized allocation will be summarized by dosing schedule, treatment group, and dose prescribed.

2.3.1 Patient disposition

Subject disposition at the end of each study epoch will be presented in table and listing. The number and percentage of subjects in each disposition category will be presented by treatment group. No statistical analysis will be presented.

The disposition table includes:

- Number of subjects screened (Screened patients)
- Number of subjects who completed the screening epoch (Screened patients)
- Number of subjects who discontinued the screening epoch (Screened patients)
- Number of subjects per each primary reason for discontinuation during the screening epoch (Screened patients)
- Number of subjects who randomized (RAN)
- Number of subjects who completed the treatment epoch (RAN)
- Number of subjects who discontinued the treatment epoch (RAN)
- Number of subjects per each primary reason for discontinuation during the treatment epoch (RAN)
- Number of subjects who entered the follow-up (RAN)

- Number of subjects who completed the follow-up (RAN)
- Number of subjects who discontinued the follow-up (RAN)
- Number of subjects per each primary reason for discontinuation during the follow-up (RAN)

Subject discontinuation might occur for the following reasons:

- AEs
- Death
- Lack of efficacy
- No longer requires treatment
- New therapy for study indication
- Non-compliance with study treatment
- Pregnancy
- Protocol deviation
- Screen failure
- Study terminated by sponsor
- Technical problems
- Lost to follow-up
- Physician's decision
- Subject/guardian decision

Protocol deviations by deviation category will be presented in table and listing separately.

A summary table will be generated to present the number and percentage of subjects included in each of the analysis sets. Subjects excluded from each of the analysis sets will also be presented in listing.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

In this study, patients will be assigned to omalizumab arm (IGE025) or placebo (PLACEBO) arm. Furthermore dose (75 to 600 mg) and dosing frequency (every 2 or 4 weeks) of the study drug will be determined by serum total IgE level (IU/mL) and body weight (kg) measured at the screening epoch according the dosing table (Table 2-2).

Table 2-2 Dosing table (mg/dose)

Baseline IgE concentration (IU/mL)	Body weight (kg)									
	≥20～25	>25～30	>30～40	>40～50	>50～60	>60～70	>70～80	>80～90	>90～125	>125～150
≥30 ～ 100	75	75	75	150	150	150	150	150	300	300
>100 ～ 200	150	150	150	300	300	300	300	300	450	600
>200 ～ 300	150	150	225	300	300	450	450	450	600	375
>300 ～ 400	225	225	300	450	450	450	600	600	450	525
>400 ～ 500	225	300	450	450	600	600	375	375	525	600
>500 ～ 600	300	300	450	600	600	375	450	450	600	
>600 ～ 700	300	225	450	600	375	450	450	525		
>700 ～ 800	225	225	300	375	450	450	525	600		
>800 ～ 900	225	225	300	375	450	525	600			
>900 ～ 1000	225	300	375	450	525	600				
>1000 ～ 1100	225	300	375	450	600		Do not dose			
>1100 ～ 1200	300	300	450	525	600					
>1200 ～ 1300	300	375	450	525						
>1300 ～ 1500	300	375	525	600						

White cell:4 weekly dosing, shaded cell:2 weekly dosing

During the treatment epoch, fexofenadine hydrochloride should be used as a concomitant medication irrespective of patient's symptoms.

- Fexofenadine hydrochloride (oral, 60 mg/time, twice per day)

In addition, in approximately 2 - 4 weeks around in March (Start date and duration will be determined by the sponsor), fluticasone propionate should be used as a concomitant medications irrespective of patient's symptoms, as well.

For patients aged ≥ 15 to < 75 years:

- Fluticasone propionate (nasal, 1 spray (50 μg)/nostril, twice per day)

For patients aged ≥ 12 to < 15 years:

- Fluticasone propionate (nasal, 1 spray (25 μg)/nostril, twice per day)

The following rescue medications are allowed to use for symptoms:

- Fexofenadine hydrochloride (only during the screening period)
- Tramazoline hydrochloride
- Levocabastine hydrochloride

2.4.1 Study treatment / compliance

A listing of study drug administration will be presented.

The listing includes; Dose prescribed, Treatment visit/ Date time/ Day of dose, Dose administered (mg), Reason, Pack number of drug dispensed in error.

The dose and regimen of study drug and the duration of exposure will be summarized for the SAF. The total number, total exposure, and duration of exposure of doses of study drug administered will be summarized by dosing schedule and treatment group. Duration of exposure to study treatment will be calculated as last visit (Day 85 date or early discontinuation) of the treatment epoch - first dose date + 1 (days).

2.4.2 Prior and concomitant therapies

Prior medication, therapy, and surgical and medical procedures for Japanese cedar pollinosis in 2016/2017 seasons will be presented in table and listing for the SAF. Furthermore, concomitant medications, and surgical and medical procedures will also be presented in table for treatment epoch only and listing for both screening and treatment epochs for the SAF.

Medications and therapies will be coded based on Anatomical Therapeutic Classification (ATC) class and PT. The number and percentage of patients having any therapy in each PT within ATC class will be presented by treatment group. Furthermore, surgical and medical procedures will be coded using the MedDRA dictionary (the latest version). The number and percentage of patients having any procedures will be summarized by SOC, PT and treatment group.

The listing includes; Medication/non-drug therapy name, Type of therapy, Reason for use, Start/End date, Dose, Unit, Frequency, Route.

2.5 Analysis of the primary objective

Primary objective of this study is to demonstrate the efficacy of omalizumab compared with placebo with respect to mean nasal symptom score during the severe symptom period.

Analyses will be based on the patients in the FAS, unless otherwise specified.

The details of each variable are described in Section 2.11.

2.5.1 Primary endpoint

The primary efficacy variable is mean nasal symptom score during the severe symptom period. The definition of the severe symptom period was described in Section 2.1.1.

As the primary efficacy variable, the mean nasal symptom score during the severe symptom period for each patient will be calculated for patients who have data for nasal symptom score for at least 50% of days during the severe symptom period.

2.5.2 Statistical hypothesis, model, and method of analysis

The mean nasal symptom score during the severe symptom period will be compared between treatments using an analysis of variance model with treatment group, dosing schedule (two-weekly or four-weekly) and randomization strata based on hypotheses below. The test will be conducted at the two-sided significance level of 5%. Least-square mean difference between treatment groups and corresponding 95% confidence interval as well as p-value will be calculated based on the model with considering a weight of the strata.

In addition, the mean nasal symptom score during the severe symptom period by treatment group will be summarized.

H0: Omalizumab is not different to placebo with respect to mean nasal symptom score over the severe symptom period.

H1: Omalizumab is different to placebo with respect to mean nasal symptom score over the severe symptom period.

Stratifications for the randomization are shown;

These variables are derived from eCRF and e-Diary data.

- Age group (< 15 years, >= 15 years)
- Coexistence of perennial allergic rhinitis (Yes/No)
- Dose frequency (every 2 weeks and 4 weeks)
- Having cedar pollinosis symptoms at the initial drug administration (Yes/No)

A proportion of patients with categorical mean nasal symptom score during the severe symptom period for each treatment group will be summarized and presented as histogram.

2.5.3 Handling of missing values/censoring/discontinuations

The mean nasal symptom score as the primary variable will be calculated for the patients who have the data of the nasal symptom score for at least 50% of days during the severe symptom period (extended if applicable). No imputation will be done for the patients who don't have the data of the nasal symptom score more than 50% of days during the severe symptom period and they will not be included in the primary analysis. It might be that the number of patients providing data to an analysis is smaller than the number of subjects in the FAS.

Handling of missing variable for secondary [redacted] analysis will be done in the same way except for analysis of JRQLQ score, [redacted] at evaluation visit.

2.5.4 Supportive analyses

Subgroup analyses

The primary analysis for the mean nasal symptom score will be repeated for the subgroups shown in Section 2.2.1. If the subgroup variable is included in the covariates of the model, it must be excluded from the model.

Supportive analysis using the adjusted nasal congestion score (AdNCS)

The primary analysis for the mean nasal symptom score will be repeated by using the AdNCS instead of symptom score for nasal congestion. The daily AdNCS is based on the study of Grouin et al. (2012) (Refer to Section 6.), and is arranged for this study associated with the characteristics of concomitant/rescue medications. The daily AdNCS is defined by the following algorithm:

[redacted]

[redacted]

Sensitivity analysis for missing data

As a sensitivity analysis for the handling of missing values for the primary analysis, if there is a greater percentage of patients without data for nasal symptom score more than 50% of days during the severe symptom period than expected as drop-out rate in the protocol (10%), imputation will be performed for the daily missing data, using multiple imputation method under Missing at Random (MAR) assumption. The analysis will be conducted using the same model as the primary variable for the patients who have at least one record of nasal symptom score during the severe symptom period in the FAS.
This approach involves three distinct steps. As the first step, multiple imputation is used to create a number of complete datasets. In Step 2, each of these datasets is analyzed by the standard procedure (here it is ANCOVA model) and in Step 3, the results of the multiple analyses are combined into a single analysis.
Since an arbitrary data missing pattern is applied, Markov chain Monte Carlo (MCMC) method assuming multivariate normality will be therefore used for imputation. The imputations will be done separately for each treatment group. Here the number of imputations will be specified to 500 and the seed to start the pseudo-random number generator will be set to 251301 for this study.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

Analyses will be based on the patients in the FAS, unless otherwise specified.

No adjustment of multiplicity will be considered for secondary endpoints.

2.7.1 Secondary endpoint

The following variables regarding each mean score of the symptoms and/or rescue medication during the severe symptom period will be analyzed;

- Mean ocular symptom score and nasal ocular symptom score
- Mean nasal symptom medication score, ocular symptom medication score, and nasal ocular symptom medication score
- Mean score for severity of sneezing, rhinorrhea and nasal congestion
- Mean score for severity of itchy and watery eye
- Mean score for impairment of daily activities
- Mean rescue medication (tramazoline hydrochloride, levocabastine hydrochloride) score

The following variables regarding symptom free days and/or rescue medication used during the severe symptom period will be analyzed;

- Number of nasal symptom free days (days with all nasal symptoms are not more than mild in severity)
- Number of ocular symptom free days (days with all ocular symptoms are not more than mild in severity)
- Number of days with no rescue medication (tramazoline hydrochloride, levocabastine hydrochloride)
- Number of nasal symptom free days with no rescue medication use (days with all nasal symptoms are not more than mild in severity and with no rescue medication: tramazoline hydrochloride)
- Amount number of rescue medication (tramazoline hydrochloride, levocabastine hydrochloride) used

The following variables at evaluation visit will be analyzed;

- Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ, No1) score

2.7.2 Statistical hypothesis, model, and method of analysis

The variables regarding each mean score of the symptoms and/or rescue medication during the severe symptom period will be analyzed using the same model as the primary variable. Least-square mean difference between treatment groups and corresponding 95% confidence interval will be calculated based on the model with considering a weight of the strata. In addition, each of these mean scores will be summarized by treatment group. Mean score for severity of sneezing, rhinorrhea, nasal congestion, itchy and watery eye will also be presented as bar graph by treatment groups.

The variables regarding symptom free days and/or rescue medication used during the severe symptom period will be analyzed by stratified Wilcoxon rank sum (van Elteren) test with dosing schedule (two-weekly or four-weekly) and randomization strata. In addition, stratified Hodges-Lehmann estimates for the median will be derived and summarized for each treatment group as well as confidence intervals for comparison between treatment groups with p-value from van Elteren test. In case only one treatment group is assigned to a stratum category, this stratum will not be considered in the analysis. Descriptive statistics for these variables will be summarized by treatment group.

A proportion of patients with categorical mean ocular and nasal ocular symptom score, a proportion of patients with categorical number of nasal or ocular symptom free days, anda proportion of patients with categorical rescue medication (tramazoline hydrochloride, levocabastine hydrochloride) free days during the severe symptom period for each treatment group will be summarized, and presented as histogram except for the proportion of patients with categorical rescue medication free days.

In addition, proportion of patients who are completely nasal symptom free during the severe symptom period defined as below will be compared between treatments using logistic regression model with treatment group, dosing schedule (two-weekly or four-weekly) and randomization strata. Odds ratio estimate and 95% confidence interval will be presented. If a parameter is not estimated due to separated or nearly separated data, Firth method based on penalized maximum likelihood will be applied for parameter estimation.

The proportion of patients who are completely nasal symptom free during the severe symptom period will be defined as: number of patients who are symptom free (all nasal symptoms are not more than mild in severity) on all non-missing days and have data for nasal symptom score for at least 18 days (i.e., up to 3 days of missing of the data will be allowed) during the 21 days of severe symptom period (if the severe symptom period is extended to more than 21 days, up to 4 days of missing of the data will be allowed to define the completely nasal symptom free patients) divided by number of patients who have data for nasal symptom score for at least 50% of days during the severe symptom period.

The analyses for the variables regarding symptom free days and/or rescue medication used during the severe symptom period above will be implemented for the patients who have data for nasal symptom score for at least 50% of days during the severe symptom period in the FAS.

The JRQLQ, No1 score at evaluation visit will be analyzed using the same model as the primary variable, and will be summarized and presented as bar graph by treatment groups.

JRQLQ, No1 score will be summarized for 3 parts: Nasal and eye symptoms (JRQLQ I), QOL-related questionnaire (JRQLQ II) mean score and 6 domain scores, and Overall face scale (JRQLQ III).

2.7.3 Handling of missing values/censoring/discontinuations

Same as the handling of missing value for the primary analysis described in Section 2.5.3 except for the analysis of JRQLQ, No1 score at evaluation visit. No imputation for missing data will be done for the secondary variables.

For counting of number of symptom free days and/or rescue medication used during the severe symptom period, the daily missing score will be treated as that there is symptom and/or rescue medication use on the day.

2.8 Safety analyses

All safety evaluations will be performed on the SAF. No imputation will be done for missing data.

2.8.1 Adverse events (AEs)

All the AEs occurring after providing written informed consent will be recorded on the Adverse Event eCRF page. For AE summaries, SOC and PT as listed by MedDRA will be used.

AEs starting during the treatment period or events present prior to the first dose of study treatment but increased in severity during the treatment period based on preferred term will be classified as treatment emergent AEs. The treatment period will be taken from the date of first drug administration to the last Visit date of treatment period (Visit 199). Overall AEs, SAEs, AEs by severity will be summarized for randomized-treatment epoch. Non-treatment emergent AEs (occurring in screening epoch) will not be summarized but listed only.

Treatment emergent AEs will be summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each SOC, having each individual AE (PT) and having each standardized MedDRA Query (SMQ). Summaries will be also presented for treatment emergent AEs by severity and for study treatment related AEs.

If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for SAE and AEs leading to discontinuation.

The FPFV and LPLV dates, the number of patients who had informed consent, treated, discontinued and had AEs related to study drug treatment will be provided by center.

The following summaries will be produced:

- Number (%) of patients reporting AEs by SOC and PT.
- Number (%) of patients reporting AEs (threshold 2%) by SOC and PT.
- Number (%) of patients reporting AEs by SOC, PT and maximum severity.
- Number (%) of patients reporting AEs suspected to be related to study drug by SOC and PT.
- Number (%) of patients reporting SAEs by SOC and PT.
- Number (%) of patients reporting AEs leading to discontinuation regardless of study drug relationship by SOC and PT.
- Number (%) of patients reporting AEs by SMQ.
- Number (%) of patients reporting AEs by SMQ and PT.

Subgroup analyses

The following summaries for the treatment emergent AEs will be repeated for the subgroups shown in Section 2.2.1.

- Number (%) of patients reporting AEs by SOC and PT.
- Number (%) of patients reporting AEs by SOC, PT and maximum severity.
- Number (%) of patients reporting AEs suspected to be related to study drug by SOC and PT.

2.8.1.1 Adverse events of special interest / grouping of AEs

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events will be done. Treatment emergent AEs of special interest and liver events for omalizumab treatment will be summarized. AEs of special interest of this study will be defined in an external file according to the latest version of eCRS and J-RMP at the DBL.

Summary tables that present numbers and percentages of patients with the AEs of special interest will be presented by risk name, seach term, preferred term and treatment.

2.8.2 Deaths

The number and percentage of patients who died will be summarized by treatment group and the principal cause in primary SOC and PT.

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, serum chemistry and urinalysis).

The following summaries will be presented:

- Descriptive summary statistics for absolute values and changes from baseline to each study visit. (Hematology, Biochemistry)
- A shift table of change from baseline to final value based on normal range. (Hematology, Biochemistry, Urinalysis)
- A shift table of change from baseline to most extreme post-baseline value based on normal range. (Hematology, Biochemistry, Urinalysis)
- Descriptive summary statistics for post-baseline maximum values and their changes from baseline in liver parameters.
- Listing of all laboratory data with the flag relative to the laboratory normal ranges.

These summaries will be presented by test group, laboratory test and treatment group. Definition of baseline and change from baseline are described in Section 2.1.1. Change from baseline will only be summarized for patients with both baseline and post baseline values.

The incidence of newly occurring notable abnormalities will be summarized for the following key parameters.

Table 2-3 Newly occurring notable laboratory test abnormalities

		Notable abnormalities	
Category	**Item**	**Low**	**High**
Hematology	Platelets	< 7.5×10^10/ L	-

Table 2-4 Newly occurring liver enzyme abnormalities

	Liver enzyme abnormalities	
Item	**Low**	**High**
ALT	-	> 3x ULN
		> 5x ULN
		> 10x ULN
		> 20x ULN
ALT or AST	-	> 3x ULN
		> 5x ULN
		> 8x ULN
		> 10x ULN
		> 20x ULN
ALT or AST, and TBL	-	ALT or AST > 3x ULN & TBL > 1.5x ULN
		ALT or AST > 3x ULN & TBL > 2x ULN
ALP	-	> 1.5x ULN
		> 2x ULN
		> 5x ULN
TBL	-	> 1x ULN
		> 1.5x ULN
		> 2x ULN
	-	ALP > 3x ULN & TBL > 2x ULN
		ALP > 5x ULN & TBL > 2x ULN
ALT or AST, TBL, and ALP	-	ALT or AST > 3x ULN & TBL > 2x ULN & ALP <= 2x ULN
ALT or AST, and symptoms	-	ALT or AST > 3x ULN & (nausea or vomiting or fatigue or general malaise or abdominal pain or rash with eosinophilia)

TBL: total bilirubin; ULN: upper limit of normal

2.8.4 Other safety data

2.8.4.1 Anti-omalizumab antibody

Anti-omalizumab antibody data will be listed for the SAF.

2.8.4.2 Vital signs

Analysis of the vital sign measurements using summary statistics will be performed.

The following summaries will be presented:

- Descriptive summary statistics for absolute values and changes from baseline to each study visit.
- Listing of all individual data including unscheduled visits.

These descriptive summaries will be presented by vital sign and treatment group. Changes from baseline will only be summarized for patients with both baseline and post-baseline values.

The following summaries will be produced:

- Systolic/ Diastolic blood pressure
- Pulse

2.9 Pharmacokinetic endpoints

Refer to PK/PD Section 2.10.

2.10 PK/PD analyses

All subjects with evaluable PK and PD parameters will be included in the data analysis.

Serum omalizumab concentration, free IgE concentration and total IgE concentration at each evaluation visits will be summarized with descriptive statistics for the PK: serum omalizmab, PD: serum free and total IgE concentration.

The following values will be calculated, and will be summarized with descriptive statistics for absolute values and %changes from baseline to each visit.

- Free IgE: 100 * (free IgE at each visit - total IgE at baseline) / total IgE at baseline
- Total IgE: 100 * (total IgE at each visit - total IgE at baseline) / total IgE at baseline
  Serum total IgE concentration is delivered in SI unit [IU/mL], while free IgE concentration is shown in [ng/mL]. All summaries will be presented in the same unit [ng/mL]. The conversion factor; 1 IU/mL = 2.42 ng/mL will be used.

No imputation for missing data will be done.

2.11 Patient-reported outcomes

In this study, The Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ, No.1), [redacted], and e-Diary are used as the patient-reported outcomes (PRO).

Refer to Section 2.7.1 and 2.13 for the details of analyses.

2.11.1 e-Diary assessment (Nasal symptoms, Ocular symptoms, Medication use, and Impairment of daily activities)

e-Diary assessment consists of nasal symptoms, ocular symptoms, medication use, and impairment of daily activities. It will be recorded by the patients everyday. If e-Diay data will be collected from 0:00 AM to 2:00 AM, they will be assigned to the previous day.

2.11.1.1 Nasal symptoms (sneezing, rhinorrhea and nasal congestion)

Nasal symptoms will be recorded by the patient everyday in their e-Diary, on a following scale of 0 (none) to 4 (intense/severe) (Table 2-5). Nasal symptom score (0-12 point) will consist of score for severity of sneezing (0-4 point), rhinorrhea (0-4 point) and nasal congestion (0-4 point).

Table 2-5 Severity of nasal symptoms

Score (/day)	4	3	2	1	0
Paroxysmal sneezing (number of episodes of paroxysmal sneezing in a day)	≥ 21 times	20-11 times	10-6 times	5-1 times	0
Rhinorrhea (number of episodes of nose blowing a day)	≥ 21 times	20-11 times	10-6 times	5-1 times	0
Nasal congestion	Completely obstructed all day	Severe nasal congestion causing prolonged oral breathing in a day	Severe nasal congestion causing occasional oral breathing in a day	Nasal congestion without oral breathing	Less severe degree than score of 1

2.11.1.2 Ocular symptoms (itchy and watery eye)

Ocular symptoms will be recorded by the patient everyday in their e-Diary, on a following scale of 0 (none) to 4 (intense/severe) (Table 2-6). Ocular symptom score (0-8 point) will consist of score for severity of itchy eye (0-4 point) and watery eye (0-4 point).

Table 2-6 Severity of ocular symptoms

Score (/day)	4	3	2	1	0
Itchy eye	More severe degree than score of 3	Frequently rubbing one's eyes	Occasionally rubbing one's eyes	not to the extent of rubbing one's eyes	None
Watery eye	More severe degree than score of 3	Frequently wiping one's tears	Occasionally wiping one's tears	not to the extent of wiping one's	None

2.11.1.3 Medication use

Medication use for Japanese cedar pollinosis (fluticasone propionate, fexofenadine hydrochloride, tramazoline hydrochloride and levocabastine hydrochloride) will be recorded by the patient everyday in their e-Diary. Medication score for nasal and ocular symptoms will be calculated as the sum of scores of medications used based on a following scale. Fexofenadine hydrochloride, an oral medication, will be counted as nasal and/or ocular medication.

Table 2-7 Score for medication use

Treatments	Score (/day)
Fluticasone propionate (nasal)	2
Fexofenadine hydrochloride (oral)	1
Tramazoline hydrochloride (nasal)	1
Levocabastine hydrochloride (ocular)	1

2.11.1.4 Impairment of daily activities

Impairment of daily activities will be recorded by the patient everyday in their e-Diary, on a following scale of 0 (none) to 4 (intense/severe) (Table 2-8).

Table 2-8 Severity of impairment of daily activities

Score (/day)	4	3	2	1	0
Impairment of daily activities*	Impossible	Painful and complicating daily life	Intermediate in degree between score of 3 and score of 1	Few troubles	Less severe degree than score of 1

* Work, study, household work, sleep, going outside, etc.

2.11.1.5 Computation rule for Variables

For the secondary endpoint (Section 2.7.1), further scores regarding each symptoms and concomitant/ rescue drug use during the severe symptom period will be calculated as below;

- Nasal ocular symptom score = Nasal symptom score + Ocular symptom score
- Nasal symptom medication score = Nasal symptom score + Medication score (Fexofenadine hydrochloride, Fluticasone propionate, Tramazoline hydrochloride)
- Ocular symptom medication score = Ocular symptom score + Medication score (Fexofenadine hydrochloride, Levocabastine hydrochloride)
- Nasal ocular symptom medication score = Nasal symptom score + Ocular symptom score + Medication score (Fexofenadine hydrochloride, Fluticasone propionate, Tramazoline hydrochloride, Levocabastine hydrochloride)

2.11.2 Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ)

The Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ, No.1) is a standard Quality of Life (QOL) Questionnaire for Japanese allergic rhinitis developed in 2002 (Practical guideline for the management of allergic rhinitis in Japan 2016). Patients rate their nasal and eye symptoms in the previous 1 - 2 weeks, as well as their impact on various aspects of their lives using a 0 to 4-point scale. The questionnaire will be completed by the patients before they see the study physician where applicable.

The JRQLQ is composed of three parts:

Nasal and eye symptoms (JRQLQ I) include six categories: Runny nose, Sneezing, Nasal congestion, Itchy nose, itchy eyes and watery eyes, on a five-point scale as 0 (no symptoms) to 4 (very severe symptoms).

Mean scores for these six categories will be determined as the nasal and eye symptom (JRQLQ I) score for each patient.

QOL-related questionnaire (JRQLQ II) include 17 items: i) Reduced productivity at work/home/school; ii) Poor mental concentration; iii) Reduced thinking power; iv) Impaired reading book/paper; v) Reduced memory loss; vi) Limitation of outdoor life (e.g. sports, picnic); vii) Limitation of going out; viii) Hesitation visiting friend or relatives; ix) Reduced contact with friends or others by telephone or conversation; x) Not an easy person to be around; xi) Impaired sleeping; xii) Tiredness; xiii) Fatigue; xiv) Frustration; xv) Irritability; xvi) Depression; and xvii) Unhappiness, on a five-point scale as 0 (no significant problem) to 4 (very greatly).

Total and mean scores for these 17 items will be determined as the QOL-related questionnaire (JRQLQ II) mean score for each patient.

In addition, these 17 items are divided into six domains including; Usual daily activities (for items i to v); Outdoor activities (for items vi and vii); Social functioning (for items viii to x); Sleep problem (for item xi); General physical problems (for items xii and xiii); and Emotional function (for items xiv to xvii).

Mean scores of items classified into each of these 6 domains will be determined as QOL-related questionnaire (JRQLQ II) domain scores for each patient.

Overall face scale (JRQLQ III) evaluates overall symptoms, condition and feelings for the past 1–2 weeks on a five-point scale from 0 (fine) to 4 (crying).

2.12 Biomarkers

Not applicable.

2.14 Interim analysis

There will be no interim analysis in this study.

A primary analysis will be performed on all the data during the screening epoch and the treatment epoch after all patients complete the treatment epoch to support the registration. The DBL for this analysis will be done after 30 days safety evaluation following the end of the treatment epoch will be completed for all patients.

After completion of post-treatment follow-up visit for all patients, anti-omalizumab antibody, PK and PD analyses for the follow-up epoch will be performed separately.

3 Sample size calculation

For the primary efficacy variable, with sample size of 155 subjects per group the study will provide 90% power to detect difference for omalizumab versus placebo. This power estimate is based on a two-sided type-I-error of 5%, a treatment difference in mean daily nasal symptom score of 0.87 and a common standard deviation of 2.35. A 0.87 treatment difference (0.29/each nasal symptom of sneezing, rhinorrhea and nasal congestion) is considered clinically relevant (Higaki et al 2013). A standard deviation of approximately 2.35 has been observed in the analysis for severe subjects in the previous study (CIGE025A1305). Assuming an early discontinuation rate of approximately 10%, a total of 346 subjects will be randomized.

Sensitivity of power to change in assumptions is summarized in Table 3-1.

Table 3-1 Sensitivity of power to change in assumptions for N=346

True treatment difference for omalizumab vs placebo (units)	SD (units)	Power for primary endpoint (2-sided alpha =5%)
		With 10% drop-out rate
0.80	2.35	84%
	2.00	93%
	2.50	80%
0.70	2.35	74%
	2.00	86%
	2.50	69%
0.60	2.35	61%
	2.00	74%
	2.50	55%
0.50	2.35	46%
	2.00	59%
	2.50	41%

4 Change to protocol specified analyses

We added followings.

Section 2.5.2 & 2.7.2

Considering a weight of the strata for least-square mean

Section 2.5.4
Supportive analysis by using the adjusted mean nasal congestion symptom score

Section 2.7.1

The variables regarding symptom free days and/or rescue medication used during the severe symptom period.

- Number of ocular symptom free days (days with all ocular symptoms are not more than mild in severity)
- Number of nasal symptom free days with no rescue medication use (days with all nasal symptoms are not more than mild in severity and with no rescue medication: tramazoline hydrochloride)

Section 2.8.1

Summary by presenting SMQ for treatment emergent AEs

Section 2.13

The variable regarding symptom severity during the severe symptom period

- Number of days with each symptom severity (most severe/ severe/ moderate/ mild/ no symptoms)

5 Appendix

5.1 Imputation rules

Refer to Section 2.5.4.

5.2 AEs coding/grading

Refer to Section 2.8.

5.3 Statistical models

The following SAS procedure will be used in this study.

PROC MIXED for the primary analysis shown in Section 2.5.2

PROC MI for the multiple imputation shown in Section 2.5.4

PROC MIANALYZE for combining of the multiple analysis results shown in Section 2.5.4

PROC NPAR1WAY for Wilcoxon rank sum (van Elteren) test shown in Section 2.7.2

PROC LOGISTIC for logistic regression analysis shown in Section 2.7.2

5.3.1 Primary analysis

Refer to Section 2.5.2.

5.3.2 Key secondary analysis

Not applicable.

5.4 Rule of exclusion criteria of analysis sets

Protocol deviation specifications (Table 5-1) and non-protocol deviation classification criteria (Table 5-2) that exclude subjects from the analysis sets are given below.

Table 5-1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
TRT01	Patient is randomized in error	RAN, FAS, PK
TRT02	Patient is randomized but no study drug is taken	FAS, SAF, PK
TRT03	Patient receives study drug but is not randomized into study	RAN, FAS, PK

Table 5-2 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RAN	TRT01, TRT03	-
FAS	TRT02	Not in RAN
SAF	TRT02	-
PK	TRT02	Not in RAN Missing of all data for PK/PD assessment

6 Reference

1. Grouin JM et all (2012), The average Adjusted Symptom Score, a new primary efficacy end-point for specific allergen immunotherapy trials. Clin Exp Allergy; 41(9):1282-8.