NOVARTIS

Global Clinical Development - General Medicine

CIGE025/Omalizumab

Clinical Trial Protocol 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

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## List of abbreviations

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|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| AR | Adverse reactions |
| AST | Aspartate Aminotransferase |
| AV | Atrioventricular |
| BMI | Body mass index |
| CABG | Coronary artery bypass graft |
| CPO | Country Pharma Organization |
| CRA | Clinical Research Associate |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organisation |
| DAR | Dosage administration record |
| DSM | Drug Supply Management |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EMA | European Medicines Agency |
| FAS | Full analysis set |
| GCP | Good Clinical Practice |
| IB | Investigator Brochure |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IgE | Immunoglobulin E |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IUD | intrauterine device |
| IUS | intrauterine system |
| IV | intravenous |
| JRQLQ | Japanese Rhinoconjunctivitis Quality of Life Questionnaire |
| LFT | Liver function test |
| MAR | Missing at Random |
| MedDRA | Medical dictionary for regulatory activities |
| MI | myocardial infarction |
| MMRM | mixed model for repeated measure |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| PRO | Patient Reported Outcome |
| QM | Quality Management |
| QoL | quality of life |
| QTcF | Fridericia QT correction formula |
| RAN | Randomized set |

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|---|---|
| RBC | Red blood cell |
| SAE | Serious Adverse Event |
| SAF | Safety set |
| SAP | Statistical analysis plan |
| SC | subcutaneous |
| SMQ | Standardized MedDRA Query |
| SoC | Standard of cares |
| SUSARs | Suspected Unexpected Serious Adverse Reactions |
| TD | Study treatment discontinuation |
| UNS | Unscheduled treatment discontinuation visit |
| WBC | white blood cell |
| WHO | World Health Organization |
| [redacted] | [redacted] |
| β-hCG | Beta Human Chorionic Gonadotropin |

## Glossary of terms

| | |
|---|---|
| Control drug | Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug |
| Dosage | Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day) |
| Electronic Data Capture (EDC) | Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces.<br>EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care. |
| Enrollment | Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol) |
| Epoch | A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up |
| Investigational drug | The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.” |
| Medication number | A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT (Interactive Response Technology) system |
| Randomization number | A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment |
| Source Data/Document | Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource. |
| Study drug/ treatment | Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy |
| Study Treatment Discontinuation (TD) | When the patient permanently stops taking study treatment prior to the defined study treatment completion date |
| Withdrawal of consent | Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material |

## Protocol summary

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| **Protocol number** | CIGE025F1301 |
| **Full Title** | 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 |
| **Brief title** | Study of efficacy and safety of omalizumab in severe Japanese cedar pollinosis adult and adolescent patients |
| **Sponsor and Clinical Phase** | Novartis / Phase III |
| **Investigation type** | Drug |
| **Study type** | Investigational |
| **Purpose and rationale** | To demonstrate the efficacy and safety of omalizumab compared with placebo, on top of standard of cares (SoC, anti-histamine and nasal corticosteroid) in adult and adolescent patients with severe Japanese cedar pollinosis, whose symptoms were inadequately controlled despite the current recommended therapies (nasal corticosteroids plus one or more medications out of anti-histamine, leukotriene receptor antagonist, or prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist) in the previous 2 Japanese cedar pollen seasons. |
| **Primary Objective(s)** | To demonstrate the efficacy of omalizumab compared with placebo with respect to mean nasal symptom score during the severe symptom period |
| **Secondary Objectives** | Objective 1: To evaluate the efficacy of omalizumab compared with placebo with respect to the following endpoints during the severe symptom period.<br>• Mean ocular symptom score and mean nasal ocular symptom score<br>• Mean nasal symptom medication score, mean ocular symptom medication score, and mean nasal ocular symptom medication score<br>• Mean score for severity of sneezing, rhinorrhea and nasal congestion<br>• Mean score for severity of itchy and watery eye<br>• Mean score for impairment of daily activities<br>• Symptom free days<br>• Use of rescue medication<br>• Japanese Rhino-conjunctivitis Quality of Life Questionnaire score<br>Objective 2: To evaluate the safety of omalizumab compared with placebo with respect to adverse events, serious adverse events, adverse events of special interest, physical examinations, laboratory assessments, vital signs and anti-omalizumab antibodies.<br>Objective 3: To evaluate the PK/PD of omalizumab with respect to serum omalizumab concentration, free IgE concentration and total IgE concentration at evaluation visits. |
| **Study design** | Randomized multi-center, double-blind, placebo-controlled study |
| **Population** | The study population consist of adult and adolescent (≥ 12 - < 75 years) patients with severe Japanese cedar pollinosis whose symptoms were inadequately controlled despite the nasal corticosteroid plus one or more medications out of anti-histamine (second generation), leukotriene receptor antagonist, or prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist in the previous 2 Japanese cedar pollen seasons. |

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| | In the study, a total of 346 patients will be enrolled in Kanto-area of Japan. Approximately 10% of the total patients enrolled will be the patients aged ≥ 12 - < 15 years at the screening epoch. Since a 10% screen failure rate is expected, approximately 390 patients will be screened. |
| **Key Inclusion criteria** | • Aged ≥ 12 - < 75 years at the screening epoch.<br>• A clinical history of Japanese cedar pollinosis defined by the following:<br>  • Took nasal corticosteroid plus one or more medications out of anti-histamine (second generation), leukotriene receptor antagonist, or prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist in Japanese cedar pollen seasons in 2016 and 2017.<br>  • Had inadequately controlled symptoms of Japanese cedar pollinosis lasting at least one week in the Japanese cedar pollen season in 2017 despite the intranasal corticosteroid plus one or more medications out of anti-histamine (second generation), leukotriene receptor antagonist, or prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist (regardless of having perennial allergic rhinitis or not).<br>• Serum cedar pollen-specific Immunoglobulin E (IgE) levels of ≥ score of 3 by CAP-RAST/FEIA, ImmunoCAP or MAST at the screening epoch.<br>• Developing a symptom of Japanese cedar pollinosis during the period from first observational day* in cedar pollen in Kanto area to initial drug administration (Visit 101), as defined by the following:<br>  • Having any nasal or ocular symptom (≥ score of 1 in sneezing, rhinorrhea, nasal congestion, itchy eye or watery eye) in at least 2 days<br>  or<br>  • Having both any nasal symptom (≥ score of 1 in sneezing, rhinorrhea, nasal congestion) and any eye symptom (≥ score of 1 in itchy eye or watery eye) in at least one day,<br>  which is confirmed by patient e-diary (unless a symptom is clearly consider to take place due to other than Japanese cedar pollinosis/allergic rhinitis (e.g., upper respiratory tract infection, or common cold)).<br>  *It will be notified to the investigator in writing by the sponsor.<br>• Body weight and serum total IgE level at screen epoch within the dosing table range; body weight of ≥ 20 to ≤ 150 kg and serum total IgE levels of ≥ 30 to ≤ 1500 IU/mL at a maximum. |
| **Key Exclusion criteria** | • With an active rhinitis other than allergic rhinitis (e.g., acute or chronic rhinitis, idiopathic rhinitis)<br>• With an active nose disease other than allergic rhinitis (e.g., acute or chronic rhinosinusitis or deflected septum) which is expected to affect the evaluation of efficacy of the study drug judged by the investigator<br>• With elevated serum IgE levels for reasons other than allergy (e.g. parasite infections, hyperimmunoglobulin E syndrome, Wiskott-Aldrich Syndrome or clinical allergic bronchopulmonary aspergillosis).<br>• With a severe asthma treated with high dose inhaled corticosteroid (≥ 800 µg/day fluticasone propionate or an equivalent for aged ≥ 16 to < 75 years, > 200 µg/day for aged ≥ 12 to < 16 years)<br>• Who are receiving operative treatment for allergic rhinitis (e.g., electrocoagulation, laser surgery, 80% trichloroacetic acid |

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| | chemo-surgery, inferior turbinectomy or posterior nasal neurectomy) within 1 years prior to the screening epoch |
| **Study treatment** | Omalizumab 150 mg, placebo |
| Efficacy assessments | • e-Diary assessment<br>  • Nasal symptom<br>  • Ocular symptom<br>  • Medication use<br>  • Impairment of daily activities<br>• JRQLQ (Japanese Rhino-conjunctivitis Quality of Life Questionnaire) |
| **Key safety assessments** | Safety of omalizumab compared with placebo with respect to adverse events, serious adverse events, adverse events of special interest, physical examinations, laboratory assessments, vital signs and anti-omalizumab antibodies |
| **Other assessments** | • [redacted]<br>• The pharmacokinetics(PK)/pharmacodynamics(PD) of Omalizumab<br>• [redacted]<br>• [redacted] |
| **Data 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 for the Full analysis set (FAS) based on hypotheses: $H_0$: Omalizumab is not different to placebo with respect to mean nasal symptom score over the severe symptom period, $H_1$: Omalizumab is different to placebo with respect to mean nasal symptom score over the severe symptom period. Adverse events will be summarized with descriptive statistics for the Safety set (SAF). The secondary efficacy variables will be basically analyzed using the same model as the primary variable for the FAS. |
| **Key words** | Add-on to standard of care, Nasal symptom score, Omalizumab, Patients aged ≥ 12 to < 75 years, Placebo-controlled, Uncontrolled severe Japanese cedar pollinosis |

# 1 Introduction

## 1.1 Background

Japanese cedar pollinosis (Japanese cedar pollen-induced seasonal allergic rhinitis) is a substantial medical problem in Japan, afflicting approximately 30% of the Japanese people. It is a type I allergic disease of the nasal mucosa, characterized by paroxysmal repetitive sneezing, watery rhinorrhea, and nasal congestion, frequently coexisting with eye symptoms (e.g., itchy eye and watery eye). It is mainly classified with two disease types of "Sneezing and rhinorrhea type" and "nasal blockage type" based on the main symptom. Japanese cedar pollen season generally starts end-January/ early-February and lasts until the end of April, in which March is the most severe (Practical guideline for the management of allergic rhinitis in Japan 2016, Okubo et al 2017).

Treatment for Japanese cedar pollinosis consists of elimination/avoidance of cedar pollen (e.g., mask, glasses), pharmacotherapy, specific immunotherapy and operative treatment (for morphological abnormality). Pharmacotherapy is chosen based on the severity and disease type of the patients. When cedar pollens begin to scatter (or when symptoms develop), treatment is initiated commonly with anti-histamine or leukotriene receptor antagonist (or prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist) and when the symptoms are exacerbated as cedar pollens scattering increases, nasal corticosteroid is added. During the peak season, patients with severe Japanese cedar pollinosis are treated with the combination of nasal corticosteroid and anti-histamine (Sneezing and rhinorrhea type) or of nasal corticosteroid, anti-histamine, and leukotriene receptor antagonist (nasal blockage type). In case of severe nasal blockage, nasal vasoconstrictor is added (Practical guideline for the management of allergic rhinitis in Japan 2016).

However, these standard of cares (SoC) are not effective enough. According to the internet survey by Okubo (Okubo and Okuda 2012), about half of the Japanese cedar pollinosis patients developed severe symptoms and even after treated with SoC, 25% of the patients still had symptoms. In addition, 10% of the patients were strongly unsatisfied with the efficacy of SoC. Such symptoms can affect quality of life (QoL) by causing fatigue, headache, cognitive impairment, and result in loss of work productivity and school days. According to the survey, 70% of cedar pollinosis patients had significantly reduced QoL. Thus, significant unmet needs are thought to remain in the treatment with Japanese cedar pollinosis.

Omalizumab (Xolair®) is a humanized monoclonal anti-Immunoglobulin E (IgE) antibody currently approved for treating inadequately controlled allergic asthma and chronic spontaneous urticaria worldwide including Japan, which selectively binds to the Ce3 domain of IgE that interacts with IgE receptors on effector cells (Presta et al 1993). This antibody blocks the binding of IgE to high-affinity receptors (FceRI), thereby preventing the IgE-mediated (type I allergic) cellular responses (Shields et al 1995, Beck et al 2004). We previously conducted randomized controlled studies with omalizumb against placebo (CIGE025A1303, Okubo et al 2006) and suplatast tosilate (CIGE025A1305, Nagakura et al 2008), which showed that omalizumab was effective and safe in patients with moderate to severe Japanese cedar pollinosis. Patients treated with omalizumab achieved a clinically relevant suppression in nasal and eye symptoms associated with the disease. The safety profile for omalizumab was consistent with the profile previously reported for the allergic asthma indication and no new safety concerns

were raised. In addition, administration of omalizumab in two consecutive Japanese cedar pollen seasons was shown to be well-tolerated and loss of efficacy was not observed (CIGE025A1306, Ogino et al 2009). Based on available data of omalizumab, it is postulated that omalizumab will have a favorable benefit to risk profile and represent a new promising treatment in patients with Japanese cedar pollinosis.

In this study, we will evaluate the efficacy and safety of omalizumab on top of SoC in patients with severe Japanese cedar pollinosis, which reflects the positioning of omalizumab expected in the treatment with Japanese cedar pollinosis.

## 1.2 Purpose

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) in adult and adolescent patients with severe Japanese cedar pollinosis, whose symptoms were inadequately controlled despite the current recommended therapies (nasal corticosteroids plus one or more medications out of anti-histamine, leukotriene receptor antagonist, or prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist) in the previous 2 Japanese cedar pollen seasons.

The results of this study will support registration of omalizumab for Japanese cedar pollinosis in Japan.

# 2 Study objectives and endpoints

## 2.1 Objectives and related endpoints

**Table 2-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary Objective(s)** | **Endpoint(s) for primary objective(s)** |
| • To demonstrate the efficacy of omalizumab compared with placebo | • Mean nasal symptom score during the severe symptom period |
| **Secondary Objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To evaluate the efficacy (symptoms, quality of life impairment) of omalizumab compared with placebo | • Mean score of the following endpoints during the severe symptom period<br>  • Ocular symptom score and nasal ocular symptom score<br>  • Nasal symptom medication score, ocular symptom medication score, and nasal ocular symptom medication score<br>  • Score for severity of sneezing, rhinorrhea and nasal congestion<br>  • Score for severity of itchy and watery eye<br>  • Score for impairment of daily activities<br>• Symptom free days (days with all nasal symptoms are not more than mild in severity) during the severe symptom period |

| Objective(s) | Endpoint(s) |
|---|---|
| | • Use of rescue medication (tramazoline hydrochloride, levocabastine hydrochloride) during the severe symptom period<br>  • Rescue medication score<br>  • Number of days with no rescue medication<br>  • Amount of rescue medication used<br>• 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]

Severe symptom period: The three weeks where the cumulative value of the mean daily nasal symptom score will be the maximum.

Severe pollen period: The period between the first and last days when ≥ 50 grains/cm$^2$ of Japanese cedar pollen are counted.

Pollen period: The start day of the pollen period is defined as the first of 2 consecutive days when ≥ 1 grain/cm$^2$ 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.

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

# 3 Investigational plan

## 3.1 Study design

This 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 $D_2$/thromboxane $A_2$ receptor antagonist) in the previous 2 Japanese cedar pollen seasons.

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

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)

**Screening epoch**

Informed consent for a patient must be obtained prior to performing any study-related assessments or collecting any data for the screening visit. For patients aged ≥ 12 - < 20 years at the screening epoch, parent or legal guardian has given written informed consent and the patient has given assent consent, if applicable.

Each patient's eligibility based on the inclusion and exclusion criteria will be determined during the screening period.

The patients should carefully record their nasal symptoms, ocular symptoms, usage of medications and impairments of daily activities on their e-diaries everyday. Only medications indicated in Section 5.5.6 and Section 5.5.7 are permitted to use for Japanese cedar pollinosis (allergic rhinitis). Fexofenadine hydrochloride and tramazoline hydrochloride for nasal symptoms, and levocabastine hydrochloride for eye symptoms are allowed to use as rescue medications.

Only one re-screening will be allowed for patients who have failed initial screening. If a patient rescreens for the study, the patient must sign a new informed consent prior to performing any study-related assessments or collecting any data and he/she will be issued a new patient number.

**Treatment epoch**

On Day 1, 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), coexisting of perennial allergic rhinitis (Yes/No), dose frequency (every 2 weeks and 4 weeks) and having cedar pollinosis symptom at the initial drug administration (Yes / No).

Doses (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 to the dosing table (Table 5-1) and must not be changed during the treatment epoch. Initial administration of the study drug will be conducted in approximately 3 weeks between mid-January and mid-February in 2018, which will be determined by the sponsor based on the

forecast of cedar pollen scattering and be notified to the investigator by the end of 2017. Allowable range of study drug administration recommended is the designated day ± 7 days. In addition, at least one-week interval will be kept between administrations.

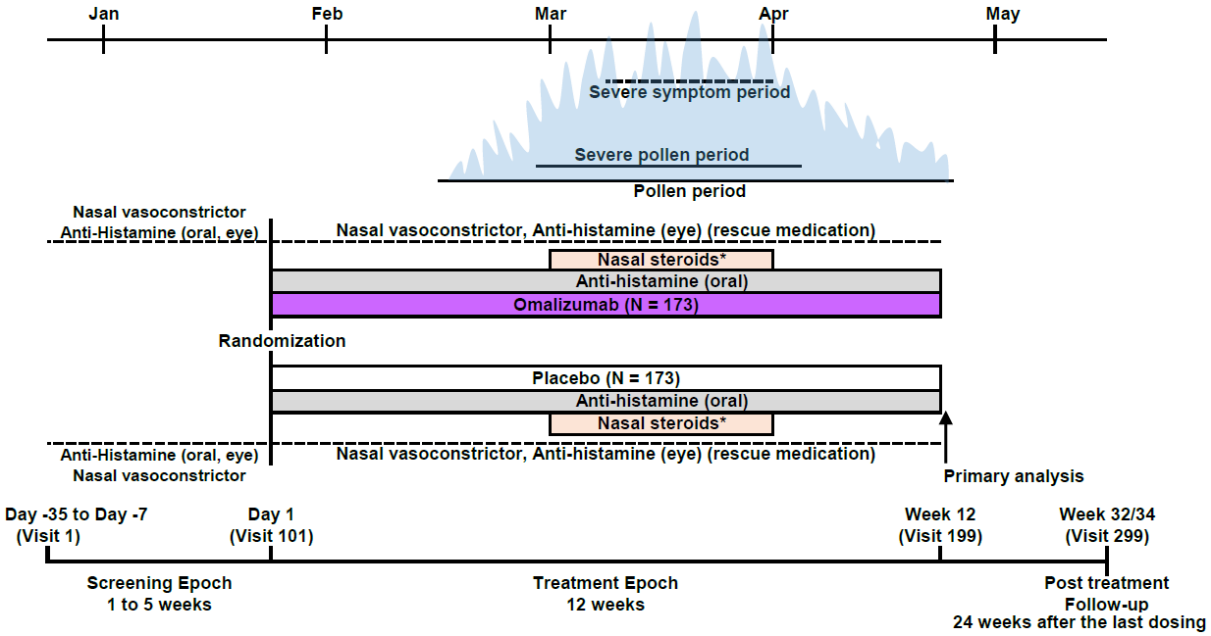
Patients are expected to attend all site visits based on the assessment schedule (Table 6-1) and to complete the entire 12 weeks duration. Patients should carefully record their nasal symptoms, ocular symptoms, usage of medications and impairments of daily activities on their e-diaries everyday.

Only medications indicated in Section 5.5.6 and Section 5.5.7 are permitted to use for Japanese cedar pollinosis (allergic rhinitis). During the treatment epoch, fexofenadine hydrochloride (oral, 60 mg/time, twice per day) should be used as a concomitant medication irrespective of patient's symptoms. In addition, in approximately 2 - 4 weeks around in March, fluticasone propionate (1 spray (50 µg for patients aged ≥ 15 to < 75 years, 25 µg for patients aged ≥ 12 to < 15 years)/nostril, twice per day) should be used as a concomitant medications irrespective of patient's symptoms, as well in ALL patients. 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 and be notified to the investigator in writing by mid-February 2018. Tramazoline hydrochloride for nasal symptom, and levocabastine hydrochloride for eye symptoms are allowed to use as rescue medications.

**Post treatment Follow-up**

Blood sampling for the follow-up assessments (anti-omalizumab antibody and Pharmacokinetics (PK)/ Pharmacodynamics (PD)) will be conducted 24 weeks after the last dosing. After the end of the treatment period, no limitation on concomitant/rescue/prohibited medications should be set.

**Figure 3-1 Study design**




*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.

## 3.2 Rationale for study design

This randomized, double-blind, parallel-group, placebo-controlled study design supports the assessment of efficacy as well as safety of omalizumab 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, leukotriene receptor antagonist, or prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist) in the previous 2 Japanese cedar pollen seasons. These patients have a significant unmet medical need and represent the target population for omalizumab.

To reflect the current recommended treatment algorithm for severe Japanese cedar pollinosis (Practical guideline for the management of allergic rhinitis in Japan 2016), this study allows to use the following treatment on the top of study treatment:

- fexofenadine hydrochloride as a concomitant medication
- fluticasone propionate as a concomitant medications in approximately 2 - 4 weeks around in March
- Tramazoline hydrochloride for nasal symptom, and levocabastine hydrochloride for eye symptoms as rescue medications.

The endpoints included in this study measure symptomatic and objective parameters of Japanese cedar pollinosis; symptomatic parameters: nasal symptoms, ocular symptoms, rescue medication use, quality of life, [redacted]; objective parameters: [redacted], which allow assessment of the suppression of Japanese cedar pollinosis symptoms by omalizumab.

The 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. See Section 3.5 and Section 9.7 for more details.

The key elements of the study were discussed and agreed with Pharmaceuticals and Medical Devices Agency in Japan.

## 3.3 Rationale for dose/regimen, route of administration and duration of treatment

### Dose/regimen, route of administration

In this study, Investigational drug (omalizumab/placebo) will be administered subcutaneously according to the dosing table, which is approved for severe allergic asthma in Japan. The rationale for using the dosing table in the study is summarized as follows;

- Allergic rhinitis and allergic asthma are both type-I allergic diseases, so same mode of action of omalizumab is expected.
- The dosing table was made based on the results of clinical studies in early phase in allergic population including asthma and rhinitis.
- There was no clinically significant difference found in PK and PD of omalizumab between allergic asthma and allergic rhinitis populations (Hayashi et al 2007).

- The dosing table (at that time) was used in all previous omalizumab studies (CIGE025A1303 (Okubo et al 2006), CIGE025A1305 (Nagakura et al 2008), CIGE025A1306 (Ogino et al 2009)) in patients with Japanese cedar pollinosis, which showed that omalizumab was effective and safe in patients with moderate to severe Japanese cedar pollinosis.

### Start date of initial treatment

Japanese cedar pollen generally begins to scatter in early-mid February indicated as Japanese cedar pollen dispersal day, defined as the first of 2 consecutive days when $\geq 1$ grain/cm$^2$ of Japanese cedar pollen is counted (average date of Japanese cedar pollen dispersal day in recent 10 years in Tokyo area is 16$^{th}$ February. But please note that very small amount pollen scatters sporadically before the Japanese cedar pollen dispersal day), scatters severely from early March to early April, and ends scattering by the end of April. On the other hand, based on the results of the nasal challenge test (Lin et al 2004), omalizumab requires approximately 1 - 2 weeks to start to show its efficacy and $\geq 4$ weeks to maximize it because omalizumab can't inhibit Immunoglobulin E (IgE), already bound to FceRI on the cell surface.

So, by setting the period of initial study drug administration in approximately 3 weeks between mid-January and mid-February in 2018, adequate time for omalizumab to exert its effect can be secured and approximately 350 study patients can initiate study treatment, as well. Because Japanese cedar pollen dispersal varies a little among years, actual period of initial treatment will be determined by the sponsor based on the forecast of cedar pollen scattering and be notified to the investigator by the end of 2017.

In addition, because omalizumab should be categorized as a "treatment drug", not "prophylactic drug", omalizumab should be administered to the patients who have already developed any symptom of Japanese cedar pollinosis defined in the inclusion criteria.

### Duration of treatment

Treatment duration of 12 weeks is selected to cover peak season for Japanese cedar pollinosis which will generally be expected from early-March to early April (and to cover almost all of the Japanese cedar pollen season (February to April)).

## 3.4 Rationale for choice of comparator

All patients will receive standard of care treatments as concomitant medications. Omalizumab or placebo will be administered as add-on therapy.

Placebo is used as comparator in this study for the following reasons:

- to allow blinding of investigators and patients to their treatment and thereby minimize bias in the evaluation of safety and efficacy assessments,
- to allow assessment of the suppression of Japanese cedar pollinosis symptoms for patients with uncontrolled disease who are treated with omalizumab, in comparison to those treated solely with standard of care treatments,
- to allow the assessment of safety of omalizumab on top of standard of care treatments compared to standard of care treatments alone.

## 3.5 Purpose and timing of interim analyses/design adaptations

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 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, PK analysis for the follow-up epoch will be performed separately.

## 3.6 Risks and benefits

The inclusion and exclusion criteria are selected to enroll patients with Japanese cedar pollinosis most likely to benefit from participating in the study. The overall risk will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring including the use of an electronic diary at home to monitor symptoms and the use of concomitant and recue medications permitted, which are in line with current medical treatment guidelines.

Omalizumab (Xolair®), an anti-IgE recombinant DNA-derived humanized monoclonal antibody, represents a unique therapeutic approach for Immunoglobulin E (IgE)-mediated disease by reducing the concentration of free IgE in blood by selectively binding to human IgE. Omalizumab has been approved for allergic asthma and chronic spontaneous urticaria worldwide including US, EU and Japan.

Identified/potential risks to omalizumab include anaphylaxis/anaphylactoid reactions, serum sickness syndrome/serum sickness like disease, antibody formation to omalizumab, Churg-Strauss syndrome/hypereosinophilic syndrome, thrombocytopenia, arterial thromboembolic events and malignant neoplasms. In clinical trials, the most commonly reported adverse reactions are injection site reactions, headaches and abdominal pain upper. Additional information on risks associated with omalizumab will be found in the local medical health authority approved product information and Investigator Brochure (IB). The risk of significant hypersensitivity reactions is mitigated by having the drug administration taking place only at the study site and requiring observation of patients at the study site after drug administration.

In summary, the benefit to the patient from study participation is that treatment with omalizumab could suppress nasal and eye symptoms of Japanese cedar pollinosis, which would be inadequately controlled despite the current recommended therapies. The risk for patients participating in this study includes the potential for known safety issues associated with omalizumab, which includes anaphylaxis, as well as for any unknown safety risks (which may be serious) that could occur. Based on available data of omalizumab, it is anticipated that omalizumab will have a favorable benefit to risk profile in patients with severe Japanese cedar pollinosis.

# 4 Population

The study population consist of adult and adolescent (≥ 12 to < 75 years) patients with severe Japanese cedar pollinosis whose symptoms were inadequately controlled despite the nasal corticosteroid plus one or more medications out of anti-histamine (second generation), leukotriene receptor antagonist, or prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist in the previous 2 Japanese cedar pollen seasons.

In the study, a total of 346 patients will be enrolled in Kanto-area of Japan. Approximately 10% of the total patients enrolled will be the patients aged ≥ 12 to < 15 years at the screening epoch. Since a 10% screen failure rate is expected, approximately 390 patients will be screened.

## 4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed. For patients aged ≥ 12 to < 20 years at the screening epoch, parent or legal guardian has given written informed consent and the patient has given assent consent, if applicable.
2. Aged ≥ 12 to < 75 years at the screening epoch.
3. A clinical history of Japanese cedar pollinosis defined by the following:
   - Took nasal corticosteroid plus one or more medications out of anti-histamine (second generation), leukotriene receptor antagonist, or prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist in Japanese cedar pollen seasons in 2016 and 2017.
   - Had inadequately controlled symptoms of Japanese cedar pollinosis lasting at least one week in the Japanese cedar pollen season in 2017 despite the use of nasal corticosteroid plus one or more medications out of anti-histamine (second generation), leukotriene receptor antagonist, or prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist (regardless of having perennial allergic rhinitis or not).

Inadequately controlled symptoms are defined as presentation of all symptoms of sneezing, rhinorrhea, and nasal congestion, at least one of which is ≥ score of 3 according to the practical guideline for the management of allergic rhinitis in Japan 2016 below (Table 4-1).

Medications for Japanese cedar pollinosis in 2016 and 2017 should be confirmed by medical records or “prescription records (book)” and symptoms of Japanese cedar pollinosis in 2017 should be confirmed by questionnaire, which should be completed by the patients at screening epoch.

**Table 4-1 Severity of nasal symptoms**

| Score | 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 |

4. Serum cedar pollen-specific IgE levels of ≥ score of 3 by CAP-RAST/FEIA, ImmunoCAP or MAST at the screening epoch.
5. Developing a symptom of Japanese cedar pollinosis during the period from first observational day* in cedar pollen in Kanto area to initial drug administration (Visit 101), as defined by the following;
   - Having any nasal or ocular symptom (≥ score of 1 in sneezing, rhinorrhea, nasal congestion, itchy eye or watery eye (Table 4-1 and Table 4-2)) in at least 2 days or
   - Having both any nasal symptom (≥ score of 1 in sneezing, rhinorrhea, or nasal congestion (Table 4-1)) and any eye symptom (≥ score of 1 in itchy eye or watery eye (Table 4-2)) in at least one day,

   which is confirmed by patient e-diary (unless a symptom is clearly consider to take place due to other than Japanese cedar pollinosis/allergic rhinitis (e.g., upper respiratory tract infection, or common cold)).
   *It will be notified to the investigator in writing by the sponsor.

**Table 4-2 Severity of ocular symptoms**

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

6. Body weight and serum total IgE level at screen epoch within the dosing table range; body weight of ≥ 20 to ≤ 150 kg and serum total IgE levels of ≥ 30 to ≤ 1500 IU/mL at a maximum.
7. ≥ 70% compliance with e-diary daily entries during the last 7 days in the screening epoch

## 4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
3. History of anaphylactic shock or severe anaphylactic reaction that in the clinical judgment of the investigator might compromise patient safety.
4. Cardiac or cardiac repolarization abnormality, including any of the following:
   - History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
   - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade Atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II and third degree AV block)
5. Patients taking medications prohibited by the protocol (see Section 5.5.8, Table 5-2)
6. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
7. Pregnant or nursing (lactating) women
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug and 30 days following the last dosing of investigational drug. Basic contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
   - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps).
   - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

9. With platelet level ≤ 100 000/μL ($100 \times 10^9$/L) at the screening epoch
10. With an active rhinitis other than allergic rhinitis (e.g., acute or chronic rhinitis, idiopathic rhinitis)
11. With an active nose disease other than allergic rhinitis (e.g., acute or chronic rhinosinusitis or deflected septum) which is expected to affect the evaluation of efficacy of the study drug judged by the investigator
12. With elevated serum IgE levels for reasons other than allergy (e.g. parasite infections, hyperimmunoglobulin E syndrome, Wiskott-Aldrich Syndrome or clinical allergic bronchopulmonary aspergillosis).
13. With a severe asthma treated with high dose inhaled corticosteroid (≥ 800 μg/day fluticasone propionate or an equivalent for aged ≥ 16 to < 75 years, >200 μg/day for aged ≥ 12 to < 16 years)
14. Who are receiving operative treatment for allergic rhinitis (e.g., electrocoagulation, laser surgery, 80% trichloroacetic acid chemo-surgery, inferior turbinectomy or posterior nasal neurectomy) within 1 years prior to the screening epoch
15. Who are taking methotrexate, gold salts, cyclosporine, tacrolimus (with the exception of topical product) or other immunosuppressant within 3 months prior to the screening epoch
16. Who are taking systemic (oral or intravenous (IV)) corticosteroids or intra-muscular depo-steroids within 4 weeks prior to the screening epoch
17. Who are receiving desensitization immunotherapy within 1 years prior to the screening epoch (excluding patients with not less than 2 years of stable maintenance doses at the screening epoch)
18. With clinically significant uncontrolled systemic disease or a history of such disease (eg., infection, hematological disease, renal, hepatic, coronary heart disease or other cardiovascular disease, cerebro-vascular, endocrinologic or gastrointestinal disease) within the previous 3 months prior to the screening epoch
19. Who have a plan to travel to Okinawa or Hokkaido in Japan or travel abroad for more than 5 days between February and April in 2018
20. Who have used omalizumab including marketed product (Xolair®).
21. Contraindications to fexofenadine hydrochloride (oral), fluticasone propionate (nasal), tramazoline hydrochloride (nasal), or levocabastine hydrochloride (ocular).

# 5 Treatment

## 5.1 Study treatment

The sponsor will provide the following investigational treatment to the study sites in open-label manner:

- Omalizumab (IGE025) 150 mg
- Placebo matching to Omalizumab (IGE025) 150 mg

### 5.1.1 Investigational and control drugs

- Name: Omalizumab (IGE025)
- Formulation: Lyophilized powder for solution for injection
- Appearance: White cake, reconstituted solution: colorless to pale yellow and clear to slightly opalescent
- Unit dose: 150 mg/vial
- Packaging: Glass vial

The appearance of omalizumab vial differs from that of placebo vial, and the viscosity of omalizumab differs from that of placebo. Omalizumab matching placebo provided in 5 ml glass vial.

### 5.1.2 Additional treatment

No additional treatment beyond investigational drug is included in this trial, except for fexofenadine hydrochloride and fluticasone propionate as concomitant medications and fexofenadine hydrochloride, tramazoline hydrochloride and levocabastine hydrochloride as rescue medications.

## 5.2 Treatment arms

Patients will be assigned at Visit 101 to omalizumab arm or placebo arm in a ratio of 1:1.

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 5-1).

A detailed schedule of administration is described in Section 6. As this is a double-blind study, the dispensing and administration of the study treatments will be performed by suitably qualified personnel who are otherwise not involved in study conduct. Further details are provided in Section 5.3, Section 5.4 and Section 5.5.

**Table 5-1 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

## 5.3 Treatment assignment and randomization

At visit "101" all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the any of the site staff.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by the age group (≥ 12 to < 15 years and ≥ 15 to < 75 years), coexisting of perennial allergic rhinitis (Yes/No), dose frequency (every 2 weeks and 4 weeks) and having cedar pollinosis symptom at the initial drug administration (Yes/No)*.

*It is estimated that approximately ≥ 70% of the randomized patients will have any symptom (≥ score of 1 in sneezing, rhinorrhea, nasal congestion, itchy eye or watery eye (Table 4-1 and Table 4-2)) at least one day of three days before initial drug administration (including the day of administration).

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Group.

## 5.4 Treatment blinding

Patients, investigator staff and personnel performing the study assessments will remain blinded to the identity of the treatment from the time of randomization until final database lock. Data

managers, programmers, statisticians, pharmacometricians and clinical experts of the Novartis clinical trial team will remain blinded until the primary analysis. An unblinded study monitor will visit the study site to monitor study drug related administration (see Section 8.1).

Blinding will be maintained using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
   - Specific vendors whose role in trial conduct requires their unblinding (e.g., IRT)
   - Drug Supply Management (DSM)
   - Unblinded pharmacist and unblinded health care professional at each study site
   - Unblinded monitor
   - Bioanalyst for PK/PD
2. The following measures will be applied to keep the patient and study personnel blinded despite differences of the investigational treatments in appearance, viscosity:
   - Study treatment will be dispensed by an unblinded pharmacist (or other authorized unblinded staff) who is independent of those involved in the assessment of study patients. In addition, the unblinded pharmacist (or other authorized unblinded staff) will store study medication and keep medication records containing unblinded information in a secure area where blinded staff would not have access.
   - Study treatments will be administered by an unblinded suitably authorized individual (health care professional) who is not responsible for any aspect of subject assessment or follow-up.
   - The independent unblinded authorized site persons (pharmacist/administrator) should not communicate the appearance, the volume and any perceived sensation associated with the administration of the investigational drug.

The procedural details relating to treatment blinding and unblinded drug administration will be described in the Pharmacist Manual and the protocol mandate tools which will be provided separately.

Unblinding will only occur in the case of patient emergencies (see Section 5.6), at the time of the primary analysis (see Section 9.7) and at the PK analysis for the follow-up epoch.

The randomization codes associated with patients/subjects from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until data base lock.

## 5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

### 5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number from the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening epoch Study Disposition CRF.

### 5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the omalizumab or placebo. Unblinded site personnel will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient,unblinded site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

### 5.5.3 Handling of study and additional treatment

#### 5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly in refrigerated conditions at 2°C to 8°C, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The unblinded site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by unblinded monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the unblinded site personnel will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis unblinded monitor or to the Novartis address provided in the investigator folder at each site.

#### 5.5.3.2 Handling of additional treatment

The following concomitant/rescue treatments has to be monitored specifically:

- Fexofenadine hydrochloride
- Fluticasone propionate

- Tramazoline hydrochloride
- Levocabastine hydrochloride

For the use of the above please refer to Section 5.5.6 and Section 5.5.7.1. Details are described in the CRF completion guidelines.

### 5.5.4 Instructions for prescribing and taking study treatment

Omalizumab or placebo will be administered by subcutaneous injection. The first administration of drug will take place at Visit 101 once all eligibility criteria have been confirmed and all other assessments performed. 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 5-1), which must not be changed during the treatment epoch. Initial administration of the study drug (Visit 101) will be conducted in approximately 3 weeks between mid-January and mid-February in 2018, which will be determined by the sponsor based on the forecast of cedar pollen scattering and be notified to the investigator in writing by the end of 2017. Allowable range of study drug administration recommended is the designated day ± 7 days. In addition, at least one-week interval will be kept between administrations. The last administration of the study drug should be at Visit 105 (Day 57) for 4-weekly dosing and at Visit 106 (Day 71) for 2-weekly dosing, respectively.

The lyophilized product takes 15 - 20 minutes to dissolve. The fully reconstituted product will appear clear or slightly opalescent and may have a few small bubbles or foam around the edge of the vial. Detailed instructions on how to reconstitute omalizumab vials can be found in the separate Pharmacist Manual. Reconstituted omalizumab vials should be protected from direct sunlight.

**Administration**

Study medication will be administered by an unblinded suitably authorized individual (qualified health care professional) who is not responsible for any aspect of subject assessment or follow-up. This individual will be identified at site as the “independent study drug administrator”. The independent study drug administrator will administer the study treatment to the corresponding patient by s.c. injection during the study visit without engaging in any unnecessary interactions that may have the potential to unblind the patient or any of the site study personnel.

Study drug is administered to the patient using a disposable 25-gauge needle and a disposable plastic tuberculin-type syringe. The injections are administered in the deltoid region on the right arm and/or left arm, avoiding urticarial lesions. Alternatively, the injections can be administered in the thigh if reasons preclude administration in the deltoid region. The injections are administered subcutaneously after aspiration of the plunger of the syringe. If blood is withdrawn, the needle is removed without administration of the dose and the injection site is changed. Study drug should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are not longer than 8 hours at 2°C to 8°C. Detailed instructions on how to administrate study drug can be found in the separate Pharmacist Manual.

After administration, patients will be observed carefully for potential adverse events of anaphylaxis at study sites (for recommendation, 2 hour observation for initial administration

and at least 30 minutes observation for administrations afterward). In addition, for a delayed onset of anaphylaxis, patients and the investigator should ensure communication means.

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment, as well as fexofenadine hydrochloride (concomitant), fluticasone propionate (concomitant), tramazoline hydrochloride (rescue), or levocabastine hydrochloride (rescue) as prescribed.

### 5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational drug dose adjustments and/or interruptions are not permitted.

If a dose (omalizumab or placebo) is dispensed by IRT but not administered to a patient at a visit at which the patient attends, this deviation event must be recorded on the Dosage Administration Record CRF.

### 5.5.6 Rescue medication

#### Screening epoch

Only the following rescue medications are allowed to use for nasal symptoms of Japanese cedar pollinosis (allergic rhinitis) during the screening epoch;

- Fexofenadine hydrochloride (oral, 60 mg/time, twice a day at maximum)
- Tramazoline hydrochloride (nasal, 2 to 3 drops/time, 4 times a day at maximum)

Patients should use these rescue medications along with the following instruction by the investigator;

If symptom of sneezing, rhinorrhea or nasal congestion not less than moderate (≥ score of 2 in Table 4-1) in severity take place, use fexofenadine hydrochloride first, then followed by tramazoline hydrochloride in case that nasal congestion doesn't improved.

For eye's symptoms (itchy and watery eye) of Japanese cedar pollinosis (allergic rhinitis), only levocabastine hydrochloride is allowed to use as a rescue medication;

- Levocabastine hydrochloride (ocular, 1 to 2 drops/time, 4 times a day at maximum)

Patients should use the medication along with the following instruction by the investigator;

If symptom of itchy eye or watery eye not less than moderate (≥ score of 2 in Table 4-2) in severity take place, use levocabastine hydrochloride.

#### Treatment epoch

During the treatment epoch, only tramazoline hydrochloride is allowed to use for nasal symptoms of Japanese cedar pollinosis (allergic rhinitis) as a rescue medication.

- Tramazoline Hydrochloride (nasal, 2 or 3 drops/time, 4 times a day at maximum)

Patients should use the medication along with the following instruction by the investigator;

If symptom of nasal congestion not less than moderate (≥ score of 2 in Table 4-1) in severity takes place despite concomitant use of fexofenadine hydrochloride or fexofenadine hydrochloride and fluticasone propionate (see Section 5.5.7), use tramazoline hydrochloride.

For eye's symptoms (itchy and watery eye) of Japanese cedar pollinosis (allergic rhinitis), only levocabastine hydrochloride is allowed to use as a rescue medication;

- Levocabastine hydrochloride (ocular, 1 to 2 drops/time, 4 times a day at maximum)

Patients should use the medication along with the following instruction by the investigator;

If symptom of itchy eye or watery eye not less than moderate (≥ score of 2 in Table 4-2) in severity take place despite concomitant use of fexofenadine hydrochloride, use levocabastine hydrochloride.

Use of rescue medication must be recorded both on the e-diary and on the Concomitant medications in the CRF.

### 5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

#### 5.5.7.1 Concomitant medications for Japanese cedar pollinosis (allergic rhinitis)

**Screening epoch**

No concomitant medications are allowed.

**Treatment epoch**

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, fluticasone propionate should be used as a concomitant medications irrespective of patient's symptoms, as well. 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 and be notified to the investigator in writing by mid-February 2018.

- Fluticasone propionate (nasal, 1 spray (50 µg)/nostril, twice per day) for patients aged ≥ 15 to < 75 years

- Fluticasone propionate (nasal, 1 spray (25 µg)/nostril, twice per day) for patients aged ≥ 12 to < 15 years

Use of concomitant medication above must be recorded both on the e-diary and on the Concomitant medications in the CRF.

For patients with asthma, long-term controlled medications should be kept constant during the screening and treatment epoch, if at all possible.

### 5.5.8 Prohibited medication

Use of the treatments displayed in the below table (Table 5-2) is NOT allowed during the period as indicated. The investigator or authorized site staff should instruct the patient to notify them about any new/additional treatments he/she takes after enrollment. All prohibited treatments taken after enrollment must be recorded in eCRF.

**Table 5-2 Prohibited medication**

| Prohibited treatments | Time period when treatment is prohibited | Action to be taken in case of use during prohibited period |
|---|---|---|
| • Nasal corticosteroids other than fluticasone propionate | a. Screening epoch<br>b. Treatment epoch | a. Discontinue patient from the trial - rescreen patient if eligible.<br>b. Discontinue study treatment if the prohibited treatments taken for more than 3 days and move to post-treatment follow-up. If not, discontinue use the prohibited treatments and continue in treatment epoch. |
| • Fluticasone propionate (nasal) | a. Screening epoch<br>b. Treatment epoch without in approximately 2 - 4 weeks around in March determined by the sponsor, when fluticasone propionate should be used as a concomitant medication | a. Discontinue patient from the trial - rescreen patient if eligible.<br>b. Discontinue study treatment if the prohibited treatments taken for more than 3 days outside the period of concomitant use and move to post-treatment follow-up. If not, discontinue use the prohibited treatments and continue in treatment epoch. |

| Prohibited treatments | Time period when treatment is prohibited | Action to be taken in case of use during prohibited period |
|---|---|---|
| • Anti-histamines other than fexofenadine hydrochloride (oral) or levocabastine hydrochloride (ocular)<br>• Leukotriene receptor antagonists<br>• Mast cell stabilizer<br>• Th2 cytokine inhibitor<br>• Prostaglandin $D_2$/thromboxane $A_2$ receptor antagonist<br>• Anti-cholinergic medication (with the exception of topical product)<br>• Combination tablet between fexofenadine hydrochloride and pseudoephedrine hydrochloride<br>• Nasal vasoconstrictor other than tramazoline hydrochloride<br>• Chinese traditional medicine prescribed for Japanese cedar pollinosis | a. Screening epoch<br>b. Treatment epoch | a. Discontinue patient from the trial - rescreen patient if eligible.<br>b. Discontinue study treatment if the prohibited treatments taken for more than 3 days and move to post-treatment follow-up. If not, discontinue use the prohibited treatments and continue in treatment epoch. |
| • Systemic corticosteroids (e.g., oral, IV, SC)<br>Note: inhaled corticosteroids are permitted but dose should be kept constant if possible | a. 4 weeks prior to screening epoch and screen epoch<br>b. Treatment epoch | a. Discontinue patient from the trial - rescreen patient after wash-out if eligible.<br>b. Discontinue study treatment and move to post-treatment follow-up. |
| • Methotrexate, gold salts, cyclosporine, tacrolimus (with the exception of topical product) or other immunosuppressant | a. 3 months prior to screening epoch and screen epoch<br>b. Treatment epoch | a. Discontinue patient from the trial.<br>b. Discontinue study treatment and move to post-treatment follow-up. |
| • Operative treatment for allergic rhinitis (e.g., electrocoagulation, laser surgery, 80% trichloroacetic acid chemo-surgery, inferior turbinectomy or posterior nasal neurectomy) | a. 1 year prior to screening epoch and screen epoch<br>b. Treatment epoch | a. Discontinue patient from the trial.<br>b. Discontinue study treatment and move to post-treatment follow-up. |
| • Desensitization immunotherapy (excluding patients with not less than 2 years of stable maintenance doses at the screening epoch) | a. 1 years prior to screening epoch and screen epoch<br>b. Treatment epoch | a. Discontinue patient from the trial.<br>b. Discontinue study treatment and move to post-treatment follow-up. |

SC: subcutaneous, IV: intravenous

In case of undue safety risk for the patient, the patient should discontinue study treatment at the discretion of the Investigator (please see Section 5.6.2).

After the end of the treatment period, no limitation on concomitant/rescue/prohibited medications should be set.

### 5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time.

## 5.6 Study completion and discontinuation

### 5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up.

For all patients a safety follow-up should be conducted (e.g. by telephone) 30 days following the end of the treatment epoch. The information to be collected at this follow up includes serious adverse events.

### 5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.6 and Section 7.5)
- Use of prohibited treatment as per recommendations in Table 5-2
- Any situation in which study participation might result in a safety risk to the patient
- A confirmed platelet level ≤ 75 000/µL ($75 \times 10^9$/L)
- Unsatisfactory therapeutic effect
- Emergence of the following adverse events: Consider any adverse events that in the judgment of the investigator, taking into account the subject's overall status, prevent the subject from continuing participation in the study
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in the "unscheduled treatment discontinuation visit" (UNS) in Table 6-1 should be completed and recorded in the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration eCRF.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should to be collected at clinic visits or via telephone visits:

- new / concomitant treatments
- adverse events / Serious Adverse Events

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

### 5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore
  and
- Does not want any further visits or assessments
  and
- Does not want any further study related contacts
  and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table below.

### 5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

### 5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

# 6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed, and an "s" indicates the data remain in the source document only.

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Patients will be contacted for safety evaluations during the 30 days following the end of the treatment epoch.

**Table 6-1 Assessment schedule**

| **Epoch** | **Screening** | **Treatment** | | | | | | | **Post-treatment follow-up** |
|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **101** | **102 [a]** | **103** | **104** | **105** | **106[a]** | **199 or TD** | **299 or TD [b]** |
| **Day** | **Day-35 to -7** | **Day 1** | **Day 15** | **Day 29** | **Day 43** | **Day 57** | **Day 71** | **Day 85** | **Day 225 or Day 239** |
| **Allowed visit window recommended (day)** | | | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **+28** |
| Obtain informed consent [c] | X | | | | | | | | |
| Inclusion/ exclusion criteria | X | X | | | | | | | |
| Demography, medical/surgical history | X | | | | | | | | |
| Complete physical exam | S | | | | | | | S | |
| Short physical exam | | S | S | S | S | S | S | | |
| Height | X | | | | | | | | |
| Weight | X | | | | | | | | |
| Vital signs | X | X | | X | | X | | X | |
| 12 lead ECG | S | | | | | | | | |
| Total IgE, specific IgE (central lab) | X | | | | | | | | |
| Contact IRT | X | X | X | X | X | X | X | X | X |
| Randomization | | X | | | | | | | |
| [redacted] | | | | | | | | | |
| PROs (JRQLQ, [redacted]) | | X | | X | X | X | | X | |
| Review patients' e-diary [d] | | S | S | S | S | S | S | S | |
| Laboratory test | | | | | | | | | |
| Pregnancy test (Urine) [e] | X | X | | X | | X | | X | |
| Hematology | X | | | X | | X | | X | |
| Chemistry | X | | | X | | X | | X | |
| Urinalysis | X | | | X | | X | | X | |

| **Epoch** | **Screening** | **Treatment** | | | | | | | **Post-treatment follow-up** |
|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **101** | **102 [a]** | **103** | **104** | **105** | **106[a]** | **199 or TD** | **299 or TD [b]** |
| **Day** | **Day-35 to -7** | **Day 1** | **Day 15** | **Day 29** | **Day 43** | **Day 57** | **Day 71** | **Day 85** | **Day 225 or Day 239** |
| **Allowed visit window recommended (day)** | | | **±7** | **±7** | **±7** | **±7** | **±7** | **±7** | **+28** |
| Sample collection | | | | | | | | | |
| PK/PD [f] | | X | | X | | X | | X | X |
| Anti-omalizumab antibody | | X | | | | | | | X |
| Drug administration | | | | | | | | | |
| Two-weekly | | X | X | X | X | X | X | | |
| Four-weekly | | X | | X | | X | | | |
| Concomitant medication/ therapy | X | X | X | X | X | X | X | X | |
| Adverse event | X | X | X | X | X | X | X | X | |
| Epoch disposition | X | | | | | | | X | X |

TD = Study treatment discontinuation
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation only
NOTE: PROs must be completed prior to other assessments.
NOTE: Unless otherwise indicated, all assessments should be performed pre-administration.
NOTE: Visit 101 should be performed in approximately 3 weeks between mid-January and mid-February in 2018, which will be will be determined by the sponsor.
NOTE: Visit 104 should be targeted between 1st March and 16th March and Visit 105 should be targeted between 17th March and 31st March, respectively. Visit 199 should be targeted on or after “FPFT (first patient first treatment) plus 12 weeks” except patients with TD.
NOTE: Allowable range of study drug administration recommended is the designated day ± 7 days. In addition, at least one-week interval will be kept between administrations.
a: Visit 102 and Visit 106 should be performed for patients with two-weekly study drug administration.
b: For patients with TD, Visit 299 should be performed 24 weeks after last administration of study drug.
c: IC obtained prior to all study specific screening procedures during or as close to the start of the screening period as possible
d: e-Diary Includes nasal symptoms (sneezing, rhinorrhea and nasal congestion), ocular symptoms (itchy and watery eye), medication use (fluticasone propionate, fexofenadine hydrochloride, tramazoline hydrochloride and levocabastine hydrochloride) and impairment of daily activities. The e-Diary will be given to patients at Visit 1, and the patients will be trained by the site staff how to use the e-Diary. The e-Diary will be completed daily (once a day) by the patients from Visit 1 to Visit 199 or TD.
e: If urine pregnancy test results at the sites are positive, dosing should be held and a serum pregnancy test will be performed by the central laboratory.
f: Pre-dose sampling at Visit 101, 103 and 105.

## 6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

## 6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity, source of patient referral, relevant medical history/current medical condition present before signing informed consent where possible, diagnoses and not symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

Information about characteristics of symptoms of Japanese cedar pollinosis in Japanese cedar pollen season in 2017 and treatments received in Japanese cedar pollen season in 2016 and 2017 will be collected.

Total IgE and specific IgE to Japanese cedar, Japanese cypress, house dusts, dermatophagoides pteronyssinus, dermatophagoides farinae, and aspergillus will be measured at the screening epoch. Lab manuals will be provided with detailed information on sample collection, handling, and shipment.

## 6.3 Treatment exposure and compliance

### 6.3.1 Omalizumab/Placebo

All doses of study treatment (omalizumab/placebo) administration will be recorded on the appropriate Dosage Administration Record eCRF page. Compliance will be assessed by unblinded field monitor at each visit using vials counts and information provided by the unblinded pharmacist or unblinded authorized site staff responsible for treatment dispensation and preparation.

### 6.3.2 Concomitant medications for Japanese cedar pollinosis

Patients are required to record in the e-diary their use of fexofenadine hydrochloride, fluticasone propionate, (tramazoline hydrochloride and levocabastine hydrochloride) on a daily basis.Compliance will be assessed by the investigator and/or study personnel at each visit using e-diary.

## 6.4 Efficacy

A number of efficacy variables will be assessed during the study. At each visit, the assessment will be started with patient reported outcomes (PROs) and then move to other assessments and

laboratory assessments. All PROs should be completed by patients before they see the study investigator for any clinical assessment or evaluation.

All patients will complete the PRO questions in the language most familiar to the respondent via an electronic tablet. Patients should be given sufficient instruction, space, time, and privacy to complete all study PROs. If patients experience any difficulties with submission after they complete the PROs, the study staff should assist them with submitting their PRO responses. Attempts should be made to collect responses to all PROs for all patients, including from those who prematurely discontinue prior to the study evaluation completion visit, however, if patients refuse to complete PROs, this should be documented in study source records. Patient's refusal to complete study PROs are not protocol deviations.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

### 6.4.1 e-Diary assessment

The patient e-diary will be provided at the screening visit and will be returned at the end of the treatment epoch. Patients should carefully record their nasal symptoms, ocular symptoms, usage of rescue medications and impairments of daily activities on their e-diaries everyday during the screening and treatment epoch (Appendix 3). The patient e-diary will be checked by a designated study staff member at each visit; in case of incomplete patient diaries, the study site staff will counsel the patient on the correct use and frequency of the patient diary.

#### 6.4.1.1 Nasal symptoms

Nasal symptoms (sneezing, rhinorrhea and nasal congestion) will be recorded by the patient everyday in their e-Diary, on a following scale of 0 (none) to 4 (intense/severe) (Table 6-2, Practical guideline for the management of allergic rhinitis in Japan 2016).

Nasal symptom score (0-12 point) consisted of score for severity of sneezing (0-4 point), rhinorrhea (0-4 point) and nasal congestion (0-4 point).

**Table 6-2 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 |

#### 6.4.1.2 Ocular symptoms

Ocular symptoms (itchy and watery eye) will be recorded by the patient everyday in their e-Diary, on a following scale of 0 (none) to 4 (intense/severe) (Table 6-3).

Ocular symptom score (0-8 point) consisted of score for severity of itchy eye (0-4 point), watery eye (0-4 point).

**Table 6-3 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 tears | None |

#### 6.4.1.3 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 based on a following scale (Table 6-4, Practical guideline for the management of allergic rhinitis in Japan 2016).

**Table 6-4 Score for medication use**

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

#### 6.4.1.4 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 6-5, Practical guideline for the management of allergic rhinitis in Japan 2016).

**Table 6-5 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.

### 6.4.2 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 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 (Appendix 4).

### 6.4.3 Appropriateness of efficacy assessments

The measures described above are standard outcome measures in trials with Japanese cedar pollinosis (allergic rhinitis).

The primary assessment is nasal symptom score, which is a validated classical mean of assessing nasal symptoms of Japanese cedar pollinosis. It is a composite score that measures symptoms of sneezing, rhinorrhea and nasal congestion based on the patient reported data collected via the e-diary. Because most Japanese cedar pollinosis patients develop eye symptoms complicated, these are assessed by using ocular symptom score based on the patient reported e-diary data, as well.

Impair quality of life (QoL) caused by symptoms of Japanese cedar pollinosis will be evaluated by using JRQLQ No.1, which is validated well-known tools in this disease area in Japan.

## 6.5 Safety

### 6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical examination will include the examination of general appearance and vital signs (Systolic blood pressure, diastolic blood pressure and pulse).

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.

### 6.5.2 Vital signs

Vital signs include blood pressure, body temperature and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured.

### 6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

### 6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected, unless otherwise specified. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

#### 6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential counts, and platelet count will be measured.

#### 6.5.4.2 Clinical chemistry

Blood urea nitrogen, creatinine, total bilirubin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, total protein, total cholesterol, albumin, uric acid, c-reactive protein, C3, C4, and CH50 will be measured.

#### 6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, PH, protein, glucose, bilirubin, ketones, and blood will be performed. Microscopy including WBC and RBC sediments will be assessed in case of an abnormal dipstick test.

#### 6.5.4.4 Anti-omalizumab antibody

Serum samples for the determination of anti-omalizumab antibodies will be collected At Visit 101, i.e. prior to first dosing, and Visit 299, i.e. 24 weeks after the last administration. The 24-week waiting period is required to ensure the elimination of omalizumab as presence of omalizumab may affect the detection of anti-omalizumab antibodies. Refer to the blood log in Appendix 6, Table 18-2 for sample collection.

### 6.5.5 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant

ECG findings at baseline must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE CRF / e(CRF) page as appropriate.

### 6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Any females with a confirmed serum positive pregnancy test during screening are not eligible for randomization.

A positive urine pregnancy test during the treatment epoch of the study requires immediate interruption of study treatment until serum Beta Human Chorionic Gonadotropin (β-hCG) is performed and found to be negative. If the serum β-hCG test is positive, study treatment must be discontinued.

### 6.5.7 Appropriateness of safety measurements

The safety assessments selected in this study are appropriate and standard for patients with Japanese cedar pollinosis and known safety profile of omalizumab.

## 6.6 Other assessments

[redacted]

### 6.6.3 Resource utilization

Not applicable.

### 6.6.4 Pharmacokinetics and pharmacodynamics

At Visits 101 (baseline), 103 (trough), 105 (trough), 199 (trough, i.e. 2 weeks after the last two-weekly dose or 4 weeks after the last four-weekly dose) and 299 (follow-up investigation) or at discontinuation, serum samples will be collected for evaluation of serum total omalizumab, free and total IgE concentration.

Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual. Also refer to the blood log in Appendix 6, Table 18-1 for sample collection.

[redacted]

# 7 Safety monitoring

## 7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of the treatment epoch. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
  - Yes
  - No
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
  - whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
  - action taken regarding [investigational] treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or

an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

## 7.2 Serious adverse events

### 7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing)) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

### 7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the end of the treatment epoch must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period following the end of the treatment epoch should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

## 7.3 Liver safety monitoring

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 has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

## 7.4 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.Study treatment errors and

uses outside of what is foreseen in the protocol will be collected in the DAR (dosage administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

**Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse**

| Treatment error type | Document in Dosage Administration record (DAR) eCRF (Yes/No) | Document in AE eCRF | Complete SAE form |
|---|---|---|---|
| Unintentional study treatment error | Yes | Only if associated with an AE | Only if associated with an SAE |
| Misuse/Abuse | Yes | Yes, | Yes, even if not associated with a SAE |

## 7.5 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up 3 months after the birth to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

# 8 Data review and database management

## 8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (ie eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.The investigator must maintain source documents for each patient in the study, consisting of case and visit notes

(hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

## 8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the EDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

## 8.3 Database management and quality control

Novartis staff (or Contract Research Organization (CRO) working on behalf of Novartis) review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data PRO data will be entered into an electronic device by the patient. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

## 8.4 Data Monitoring Committee

Not required.

## 8.5 Adjudication Committee

Not required.

# 9 Data analysis

The primary analysis will be conducted on all subject data at the time the treatment epoch ends. The PK 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.

## 9.1 Analysis sets

The following analysis sets will be used in this study;

**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 evaluable PK/PD data. 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.

## 9.2 Patient demographics and other baseline characteristics

Demographic, background data and key efficacy variables at baseline will be summarized for the RAN 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.

Summaries will be provided for age, gender, race, ethnicity, baseline height, weight, body mass index (BMI), and relevant medical history. More detail of variables will be defined in statistical analysis plan (SAP). No imputation will be done for missing data.

Baseline will be defined as the last measurement before or at the randomization visit.

No statistical analysis will be provided for baseline comparability between the treatment groups.

## 9.3 Treatments

A listing of study drug administration will be presented. The total number of doses of study drug administered will be summarized by dosing schedule and treatment group for the SAF. The dose and regimen of study drug and the duration of exposure will also be summarized for the SAF. 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).

Concomitant medications and non-drug therapies used will be coded, listed, and summarized for the SAF

## 9.4 Analysis of the primary variable(s)

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

### 9.4.1 Primary Variable(s)

The primary efficacy variable is mean nasal symptom score during the severe symptom period.

The severe symptom period will be defined as: the three weeks where the cumulative value of the mean daily nasal symptom score will be the maximum, if it meets 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 meets one of the criteria above.

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 will be divided by the non-missing number of patients per day. The severe symptom period will be the same for all patients.

The severe symptom period will be specified during blinded review. The detail rule of definition for the severe symptom period will be described in statistical analysis plan (SAP).

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

The analysis of the primary efficacy variable using the FAS will be the primary basis of conclusion.

### 9.4.2 Statistical model, hypothesis, 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 will be calculated based on the model.

$H_0$: Omalizumab is not different to placebo with respect to mean nasal symptom score over the severe symptom period.

$H_1$: Omalizumab is different to placebo with respect to mean nasal symptom score over the severe symptom period.

### 9.4.3 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 and [redacted] at evaluation visit.

### 9.4.4 Sensitivity analyses

As a sensitivity analysis to the handling of missing values for the primary analysis, if we have more number of patients who don't have the data of the 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 missing data, e.g., 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 FAS and detail of imputation method will be described in statistical analysis plan (SAP).

## 9.5 Analysis of secondary variables

Analyses will be based on the patients in the FAS. No imputation for missing data will be done for secondary variables.

No adjustment of multiplicity will be considered for secondary endpoints.

### 9.5.1 Efficacy variables

The following variables 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.

- 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 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.

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

The following variable at evaluation visit will be analyzed using the same model as the primary variable. Basically the evaluation visit will be the visit during the severe symptom period and detail rule for definition of the evaluation visit will described in statistical analysis plan (SAP).

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

### 9.5.2 Safety variables

All safety evaluations will be performed on the SAF.

#### Adverse events

All the AEs occurring after providing written informed consent will be recorded on the Adverse Event eCRF page. AEs starting on or after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term will be classified as treatment emergent AEs. 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 primary system organ class and having each individual AE (preferred term). 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 death, SAE, and AEs leading to discontinuation.

Treatment emergent AEs of special interest for omalizumab treatment will be also summarized. AEs of special interest for omalizumab treatment will be specified as compound-level risk factors defined in the Case Retrieval Strategy.

Summary tables that present numbers and percentages of patients with the AEs of special interest will be presented by standardized MedDRA Query (SMQ) (if applicable), preferred term and treatment.

#### Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, serum chemistry and urinalysis). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values.

#### Anti-omalizumab antibody

A summary of anti-omalizumab antibody data will be provided.

#### Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values.

### 9.5.3 Resource utilization

Not applicable.

### 9.5.4 Pharmacokinetics

Refer to PK/PD Section 9.5.7.

### 9.5.5 DNA

Not applicable.

### 9.5.6 Biomarkers

Not applicable.

### 9.5.7 PK/PD

Serum omalizumab concentration, free IgE concentration and total IgE concentration at each evaluation visits will be summarized with descriptive statistics for the PK. No imputation for missing data will be done.

## 9.7 Interim analyses

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 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, PK analysis for the follow-up epoch will be performed separately.

## 9.8 Sample size calculation

For 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 9-1.

**Table 9-1 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<br>2.00<br>2.50 | 84%<br>93%<br>80% |
| 0.70 | 2.35<br>2.00<br>2.50 | 74%<br>86%<br>69% |
| 0.60 | 2.35<br>2.00<br>2.50 | 61%<br>74%<br>55% |
| 0.50 | 2.35<br>2.00<br>2.50 | 46%<br>59%<br>41% |

# 10 Ethical considerations

## 10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

## 10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of

the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

## 10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

## 10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## 10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess Good Clinical Practice (GCP) compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures, and are performed according to written Novartis processes.

# 11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and

not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

## 11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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References are available upon request.

# 13 Appendix 1: Clinically notable laboratory values and vital signs

Refer to Appendix 2 for clinically notable laboratory values for hepatotoxicity.

The following other specific criteria have been identified for this study:

- Platelets < 75 000/µL

The following actions must be taken if the specific value in platelet counts are observed:

- In case of a platelet count < 75 000/µL ($75 \times 10^9$/L) is detected, further dosing must be suspended and a second 'retest' blood-sample must be taken immediately (recommended within 1 - 2 days).
- If the second ('re-test') blood sample confirms a platelet count < 75 000/µL ($75 \times 10^9$/L), the patient should discontinue the study treatment and will be followed as clinically appropriate.
- If the second sample does not confirm the low platelet count, the patient will continue to receive study medication as scheduled, following discussion with Clinical Trial Leader at Novartis.

The Central Laboratory will flag laboratory values falling outside of the normal ranges on the Central Laboratory Report. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate eCRF.

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

# 14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

**Table 14-1 Liver Event and Laboratory Trigger Definitions**

| | Definition/ threshold |
|---|---|
| LIVER LABORATORY TRIGGERS | • 3 × ULN < ALT / AST ≤ 5 × ULN<br>• 1.5 × ULN < TBL ≤ 2 × ULN |
| LIVER EVENTS | • ALT or AST > 5 × ULN<br>• ALP > 2 × ULN (in the absence of known bone pathology)<br>• TBL > 2 × ULN (in the absence of known Gilbert syndrome)<br>• ALT or AST > 3 × ULN and INR > 1.5<br>• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN (mainly conjugated fraction) without notable increase in ALP to > 2 × ULN)<br>• Any clinical event of jaundice (or equivalent term)<br>• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia<br>• Any adverse event potentially indicative of a liver toxicity* |

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

**Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers**

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| Potential Hy's Law case[a] | • Discontinue the study treatment immediately<br>• Hospitalize, if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| **ALT or AST** | | |
| > 8 × ULN | • Discontinue the study treatment immediately<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 3 × ULN and INR > 1.5 | • Discontinue the study treatment immediately<br>• Hospitalize, if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 5 to ≤ 8 × ULN | • Repeat LFT within 48 hours<br>• If elevation persists, continue follow-up monitoring<br>• If elevation persists for more than 2 weeks, discontinue the study drug<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| > 3 × ULN accompanied by symptoms[b] | • Discontinue the study treatment immediately<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 3 to ≤ 5 × ULN (patient is asymptomatic) | • Repeat LFT within the next week<br>• If elevation is confirmed, initiate close observation of the patient | Investigator discretion<br>Monitor LFT within 1 to 4 weeks |
| **ALP (isolated)** | | |
| > 2 × ULN (in the absence of known bone pathology) | • Repeat LFT within 48 hours<br>• If elevation persists, establish causality<br>• Complete liver CRF | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| **TBL (isolated)** | | |
| > 2 × ULN (in the absence of known Gilbert syndrome) | • Repeat LFT within 48 hours<br>• If elevation persists, discontinue the study drug immediately<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)<br>Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated (indirect) bilirubin) |
| > 1.5 to ≤ 2 × ULN (patient is asymptomatic) | • Repeat LFT within the next week<br>• If elevation is confirmed, initiate close observation of the patient | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| Jaundice | • Discontinue the study treatment immediately<br>• Hospitalize the patient<br>• Establish causality<br>• Complete liver CRF | ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| Any AE potentially indicative of a liver toxicity* | • Consider study treatment interruption or discontinuation<br>• Hospitalization if clinically appropriate<br>• Establish causality<br>• Complete liver CRF | Investigator discretion |

[a] Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b] (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

# 15 Appendix 3: Patient e-Diary (sample)

Please complete the following questions about Japanese cedar pollinosis once each day during the screening and treatment epoch (preferably at the same time each day).

- Today's Date:

1. Please rate each of your nasal symptoms of Japanese cedar pollinosis today (please select only one response).

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

2. Please rate each of your ocular symptoms of Japanese cedar pollinosis today (please select only one response).

| | |
|---|---|
| Itchy eye | Score 4: More severe degree than score of 3 |
| | Score 3: Frequently rubbing eye(s) |
| | Score 2: Occasionally rubbing eye(s) |
| | Score 1: Not to the extent of rubbing eye(s) |
| | Score 0: None |
| Watery eye | Score 4: More severe degree than score of 3 |
| | Score 3: Frequently wiping tears |
| | Score 2: Occasionally wiping tears |
| | Score 1: Not to the extent of wiping tears |
| | Score 0: None |

3. Please rate the impairments of your daily activities caused by Japanese cedar pollinosis today (please select only one response).

| | |
|---|---|
| Impairment of daily activities | Score 4: Impossible |
| | Score 3: Painful and complicating daily life |
| | Score 2: Intermediate in degree between score of 3 and score of 1 |
| | Score 1: Few troubles |
| | Score 0: Less severe degree than score of 1 |

4. Please record the usage of the following medications for Japanese cedar pollinosis today.

| | |
|---|---|
| Fexofenadine hydrochloride (oral) | Number of tablets taken in the morning |
| | Number of tablets taken in the evening |
| Fluticasone propionate (nasal) | Number of rhinenchysis in the morning |
| | Number of rhinenchysis in the evening |
| Tramazoline hydrochloride (nasal) | Number of rhinenchysis in a day |
| Levocabastine hydrochloride (ocular) | Number of ocular instillation in a day |

# 16 Appendix 4: Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ)

Japanese Rhino-conjunctivitis Quality of Life Questionnaire
(JRQLQ No1)

To patients with allergic rhinitis (including pollinosis)

These days, the aim of medical treatment is not just to cure disease but also to give patients a better quality of life. The purpose of this survey is to determine to what extent your rhinitis interferes with your life and whether it would be improved by treatment. As with all medical treatment, the information you provide in this survey will remain strictly confidential.

You may find some of the following questions difficult to answer, but just answer to the best of your ability.

I. Tick the box that best describes the severity of the worst nasal and eye symptoms you have experienced in the past 1 - 2 weeks.

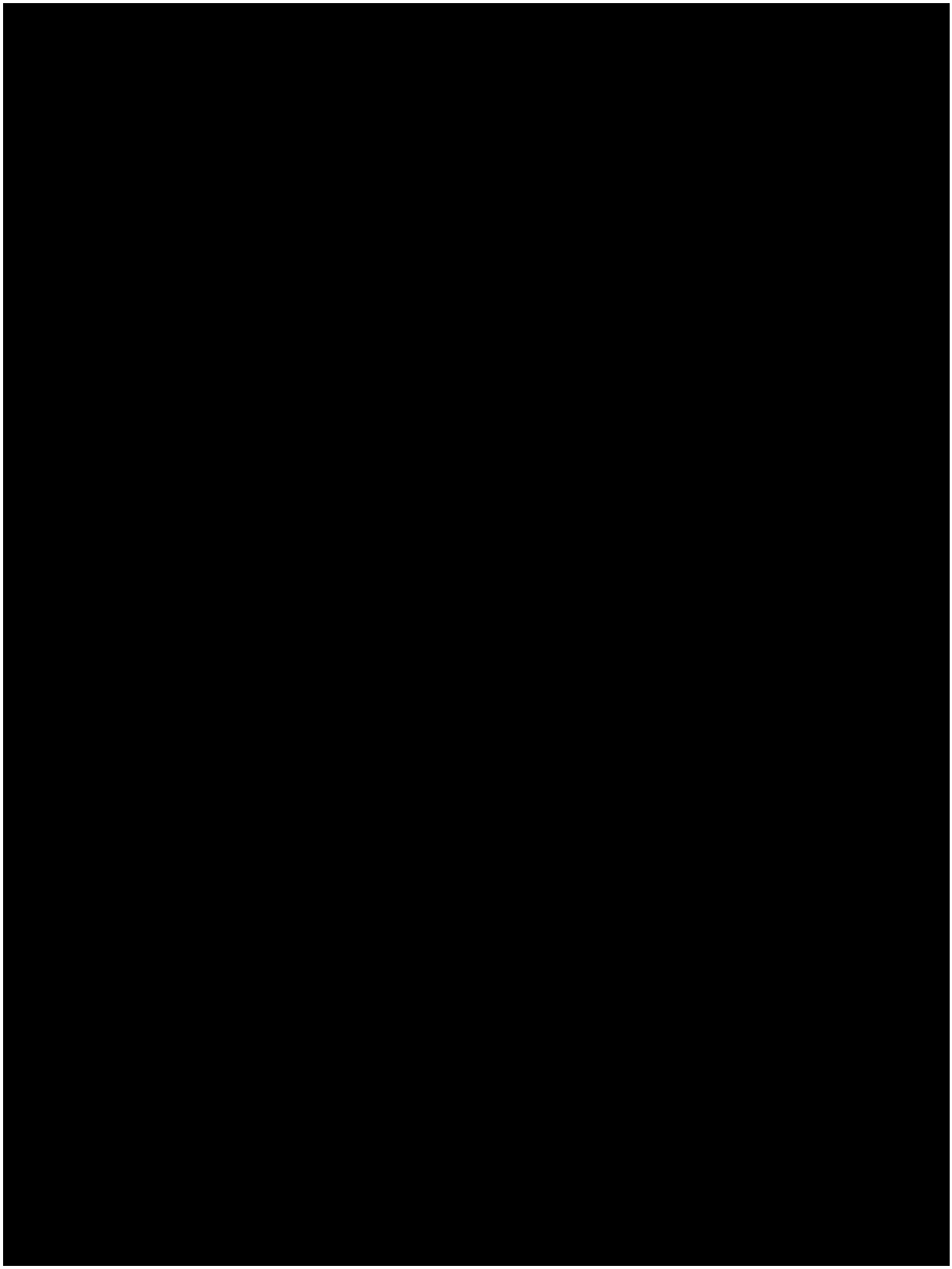
| Nasal and eye symptoms | 0, No symptoms | 1, Mild | 2, Moderate | 3, Severe | 4, Very severe |
|---|---|---|---|---|---|
| Runny nose | □ | □ | □ | □ | □ |
| Sneezing | □ | □ | □ | □ | □ |
| Blocked nose (nasal congestion) | □ | □ | □ | □ | □ |
| Itchy nose | □ | □ | □ | □ | □ |
| Itchy eyes | □ | □ | □ | □ | □ |
| Watery eyes | □ | □ | □ | □ | □ |

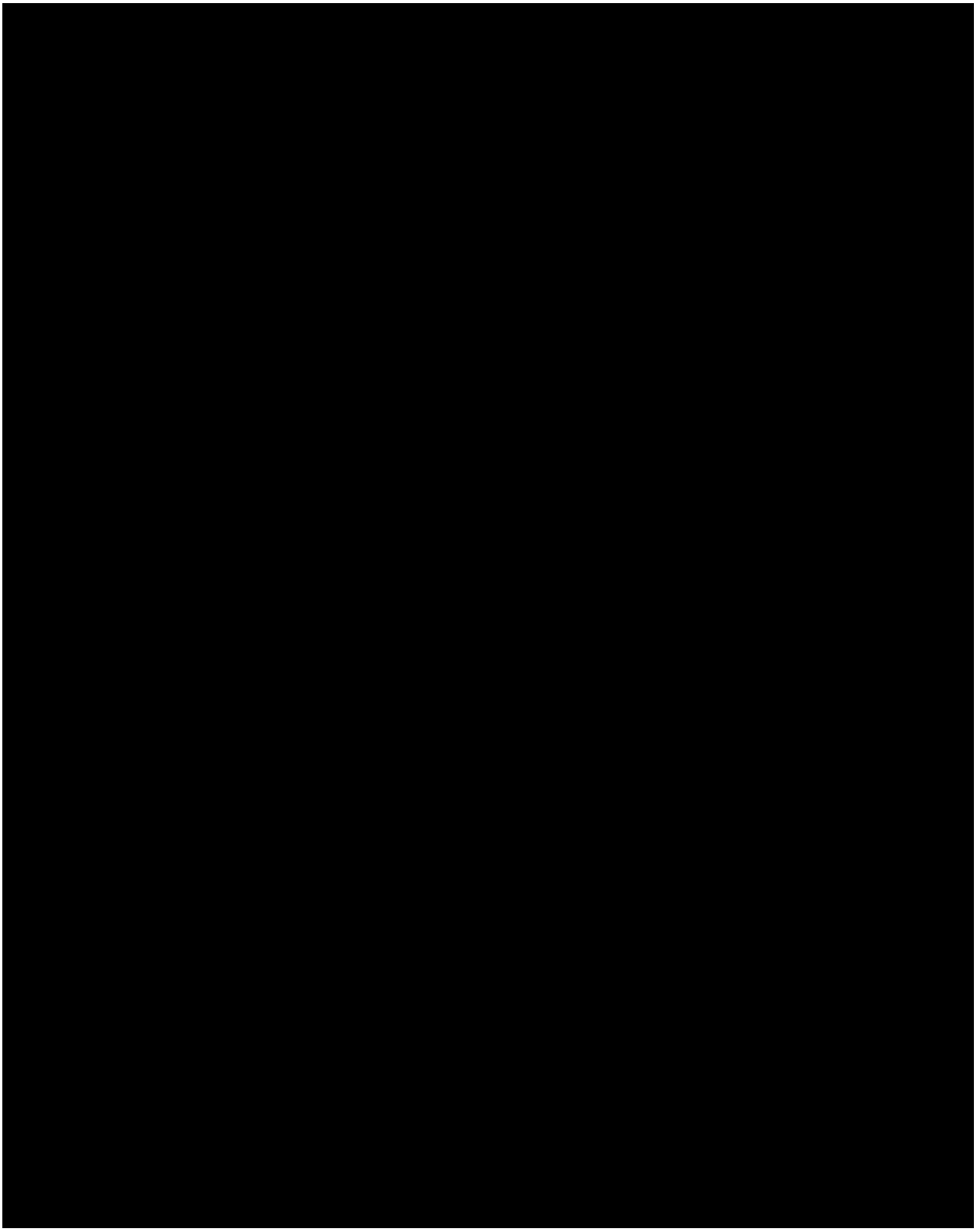
II. Tick the box that best describes the worst extent to which the symptoms in I above have interfered with your quality of life in the past 1 - 2 weeks. If any of the items listed under Quality of life below definitely do not relate to the symptoms in I (nose, eye). then there is no need to tick a box for that particular item.

| Quality of life | 0, No | 1, Yes, slightly | 2, Yes, moderately | 3, Yes, greatly | 4, Yes, very greatly |
|---|---|---|---|---|---|
| 1. Reduced productivity at work/home | □ | □ | □ | □ | □ |
| 2. Poor mental concentration | □ | □ | □ | □ | □ |
| 3. Reduced thinking power | □ | □ | □ | □ | □ |
| 4. Impaired reading book / newspaper | □ | □ | □ | □ | □ |
| 5. Reduced memory | □ | □ | □ | □ | □ |
| 6. Limitation of outdoor life (e.g. sport, picnics) | □ | □ | □ | □ | □ |
| 7. Limitation of going out | □ | □ | □ | □ | □ |
| 8. Hesitation visiting friend or relatives | □ | □ | □ | □ | □ |
| 9. Reduced contact with friends or others by telephone or conversation | □ | □ | □ | □ | □ |
| 10. Not an easy person to be around | □ | □ | □ | □ | □ |
| 11. Impaired sleeping | □ | □ | □ | □ | □ |
| 12. Tiredness | □ | □ | □ | □ | □ |
| 13. Fatigue | □ | □ | □ | □ | □ |
| 14. Frustration | □ | □ | □ | □ | □ |
| 15. Imitability | □ | □ | □ | □ | □ |
| 16. Depression | □ | □ | □ | □ | □ |
| 17. Depression | □ | □ | □ | □ | □ |

III. Please circle the number of the face that best describes your general state (including your symptoms, life and emotion) in the past 1 - 2 weeks.


Okubo K, Kurono Y, Ichimura K, et al (2017) Japanese guidelines for allergic rhinitis 2017. Allergol Int; 66(2):205-19.





# 18 Appendix 6: Blood log

**Table 18-1 Blood log for PK and PD Samples**

| | **Omalizumab** | | **Total IgE** | | **Free IgE** | |
|---|---|---|---|---|---|---|
| Matrix | Serum | | Serum | | Serum | |
| Name and type of analysis | PK | | PD | | PD | |
| Visit | Dose Reference ID | Sample Number | Dose Reference ID | Sample Number | Dose Reference ID | Sample Number |
| Visit 101 pre-dose | 1 | 101 | 1 | 201 | 1 | 301 |
| Visit 103 pre-dose | 3 | 102 | 3 | 202 | 3 | 302 |
| Visit 105 pre-dose | 5 | 103 | 5 | 203 | 5 | 303 |
| Visit 199 14 days or 28 days post dose | 6 | 104 | 6 | 204 | 6 | 304 |
| Visit 299 168 days post treatment | 6 | 105 | 6 | 205 | 6 | 305 |

**Table 18-2 Blood log for immunogenicity**

| | **Immunogenicity** | |
|---|---|---|
| Matrix | Serum | |
| Visit | Dose Reference ID | Sample Number |
| Visit 101 (pre-dose) | 1 | 401 |
| Visit 299 168 days post treatment | 6 | 402 |