

**Official Title:** Open-Label Extension Study of Omalizumab in Patients With Chronic Rhinosinusitis With Nasal Polyps

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## STATISTICAL ANALYSIS PLAN

**TITLE:** OPEN-LABEL EXTENSION STUDY OF OMALIZUMAB IN PATIENTS WITH CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

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## STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
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## **1. BACKGROUND**

The overall purpose of the analyses outlined in this Statistical Analysis Plan (SAP) is to evaluate the safety, efficacy and durability of response of omalizumab in an open-label setting in adult patients with chronic rhinosinusitis with nasal polyps (CRSwNP) who have completed the double-blind placebo-controlled Phase III Studies GA39688 or GA39855.

## **2. STUDY DESIGN**

This study is an open-label clinical study. Patients who had completed the treatment period of Studies GA39688 or GA39855 and fulfilled the eligibility criteria for the open-label extension study were enrolled.

### **2.1 PROTOCOL SYNOPSIS**

The Protocol Synopsis is in [Appendix 1](#). For additional details, see the Schedule of Assessments in [Appendix 2](#).

### **2.2 OUTCOME MEASURES**

#### **2.2.1 Primary Safety Endpoints**

- Incidence of serious and non-serious adverse events
- Incidence of adverse events leading to omalizumab discontinuation.

#### **2.2.2 Secondary Safety Endpoints**

- Clinically significant change in laboratory values.

#### **2.2.3 Primary Efficacy Endpoints**

- Change from baseline at Weeks 4, 8, 16, 24, 36, 52, 64 and 76 in Nasal polyp score (NPS)
- Change from baseline at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72 and 76 in nasal blockage/congestion score (NCS)

#### **2.2.4 Secondary Efficacy Endpoints**

- Change from baseline at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72 and 76 in the following assessments:
  - Total nasal symptom score (TNSS)
  - Posterior rhinorrhea (PRS), also known as post-nasal drip
  - Anterior rhinorrhea (ARS), also known as runny nose
  - Loss of sense of smell
- Change from baseline at Weeks 4, 8, 16, 24, 36, 52, 64 and 76 in SNOT-22
- Change from baseline at Weeks 4, 8, 16, 24, 36, 52, 64 and 76 in AQLQ (patients with comorbid asthma only)

- Change from baseline at Weeks 16, 24, 36, 52, 64 and 76 in EQ-5D-5L
- Change from baseline at Weeks 8, 16, 24, 36, 52, 64 and 76 in UPSIT

### **2.2.5 Exploratory Efficacy Endpoints**

- Reduction in the need for surgery by Weeks 36 and 52, as defined by an NPS of  $\leq 4$  (unilateral score of  $\leq 2$  on each side) for patients who had an NPS of  $\geq 5$  at start of parent studies, along with an improvement in SNOT-22 score of  $\geq 8.9$
- Requirement of rescue treatment (systemic CS for  $\geq 3$  consecutive days) or having had surgery for nasal polyps through Week 52
- Requirement of rescue treatment (systemic CS for  $\geq 3$  consecutive days) through Week 52
- Having had surgery for nasal polyps through Week 52
- Change from Week 24 at Weeks 36, 52, 64, and 76 in MOS Sleep Scale
- Change from Week 24 at Weeks 36, 52, 64 and 76 in Healthy Days Core Module

### **2.2.6 Exploratory Psychometric Endpoints**

- Patient Global Impression of Change at Weeks 36, 52, 64 and 76.

## **2.3 DETERMINATION OF SAMPLE SIZE**

As this study is an open-label extension (OLE) of previous studies (Studies GA39688 and GA39855), no formal sample size calculation was performed. The two parent studies (Studies GA39688 and GA39855) had a combined sample size of 265 randomized patients in total. Of the 265 patients, 249 patients are enrolled into this open-label extension study.

## **2.4 ANALYSIS TIMING**

Two interim safety analyses have been conducted in support of marketing application to Health Authorities for the CRSwNP indication. The first interim safety analysis took place after the last study visits for both Studies GA39699 and GA39855. The second interim safety analysis was performed to support the 120-day safety update following the submission of the marketing application.

The final analysis will take place after the last patient's last visit.

## **3. STUDY CONDUCT**

### **3.1 RANDOMIZATION**

This study is an OLE clinical study. Patients who had completed the treatment period of Studies GA39688/GA39855 and fulfill the eligibility criteria for the OLE study were

eligible to enroll. All enrolled patients had received 28 weeks of dosing of open-label omalizumab before entering a 24-week off-treatment observation phase of the study. Omalizumab dose during the 28 weeks open-label treatment was determined based on serum total IgE levels and body weight from the screening data from the parent studies. No randomization was used for the OLE study.

## **3.2 DATA MONITORING**

All safety events will be closely monitored by the study team. The Sponsor followed the U.S. FDA guidance ([FDA 2006](#)) to evaluate the need for an independent Data Monitoring Committee (iDMC) and decided not to have an iDMC for this study based on the criteria mentioned in the guidance. Given the established safety record of omalizumab, the nature of nasal polyposis, and the outcomes being examined, an iDMC is not indicated for this study.

### **3.2.1 Anaphylaxis Adjudication Committee**

All potential anaphylaxis cases reported by investigators to the Sponsor will be subsequently submitted for adjudication to a three-member anaphylaxis adjudication committee composed of external experts in allergic diseases. The committee will assess whether the reported event is a true anaphylaxis event (based on Sampson's criteria; see [Appendix 3](#)) and whether the reported anaphylaxis event is causally related to study drug. Further details will be provided in the Anaphylaxis Adjudication Charter.

## **4. STATISTICAL METHODS**

### **4.1 ANALYSIS POPULATIONS**

#### **4.1.1 Efficacy Population**

All efficacy analyses will be based on the full analysis set of the OLE study (FAS-OLE), consisting of all patients enrolled into this OLE grouped according to the treatment assigned (omalizumab or placebo) at randomization of the previous studies. Patients who were not enrolled in the OLE study, their parent study data will not be included in the analyses.

#### **4.1.2 Efficacy Analysis Cohorts**

The study populations will consist of two cohorts:

- Cohort A: Study participants who have completed Study GA39688 grouped according to treatment randomized in Study GA39688 (omalizumab or placebo) and who have enrolled into the current study
- Cohort B: Study participants who have completed Study GA39855 grouped according to treatment randomized in Study GA39855 (omalizumab or placebo) and who have enrolled into the current study

If no meaningful differences exist between cohorts with respect to baseline characteristics and efficacy results from Studies GA39688 and GA39855 appear to be



consistent, the cohorts will be pooled for all efficacy analyses according to the treatment assigned at randomization in Studies GA39688 and GA39855. In addition, the co-primary endpoints, NSC and NPS, from the parent studies, will be presented separately by cohort.

#### **4.1.3      Safety Population**

All safety analyses will be based on the subset of the full analysis set of the OLE study (FAS-OLE), who received at least one dose of omalizumab in the OLE study (Safety-OLE), grouped according to the treatment received (omalizumab or placebo) in the parent studies:

- Placebo: Patients who received only and at least one placebo injections during the parent studies' treatment period.
- Omalizumab: Patients who received at least one omalizumab injection during the parent studies' treatment period.

### **4.2              DATA HANDLING CONVENTIONS**

#### **4.2.1      Definition of Baseline**

Unless otherwise specified, baselines for all efficacy endpoints (NPS, NCS, TNSS, loss of sense of smell, PRS, ARS, SNOT-22, UPSIT, EQ-5D-5 and AQLQ), total IgE and all other non-efficacy assessments (free IgE, vital signs, lab assessment) are defined as on or prior to the date of randomization in the parent studies (see GA39688/GA39855 SAP). This baseline will be referred as the baseline at randomization.

The baseline at OLE enrollment is defined as the Week 24 visit of the parent studies, except for nasal symptoms (interview), Medical Outcomes Study (MOS) Sleep Scale, Health Days Core Module, weight, vital signs and concomitant medications, which are collected during OLE Week 24 visit. The data collected at this baseline will be summarized only; no change from baseline analysis will be performed using this baseline, except for MOS Sleep Scale and Healthy Days Core Module, which are not collected in the parent studies.

#### **4.2.1.1      Analysis Timepoints and Windows**

Given that patients were eligible for enrollment within 28 days after Week 24 visit of the Studies GA39688/GA39855, analysis timepoints and windows for this OLE study are adjusted using the first dose of the open-label drug as the new reference point (OLE Week 24).

In addition, analysis timepoints for the parent studies are derived from data collected in the parent studies only and analysis timepoints for the OLE study are derived from data collected in the OLE study only, that is, data collected on a particular day can only contribute to either the parent studies or the OLE study, but not both parent studies and the OLE study.

The analysis time windows for safety, efficacy, pharmacodynamic, or pharmacokinetic assessment are listed in [Table 1](#). All data collected within the specified window of a planned timepoint study day will be considered for an assigned timepoint for analysis. Within an interval for a given planned visit day, the assessment with the date nearest to the planned timepoint study day (for that assessment) will be selected, with assessments occurring prior to the planned timepoint study day taking priority in case of a tie.

**Table 1 Analysis Timepoints and Windows**

<b>Analysis Timepoints</b>	<b>First Study Day Included (-13 days)</b>	<b>Planned Timepoint Day</b>	<b>Last Study Day Included (+14 days)</b>
Week 4 <sup>‡</sup>	15	28	42
Week 8 <sup>‡</sup>	43	56	70
Week 12 <sup>‡</sup>	71	84	98
Week 16 <sup>‡</sup>	99	112	126
Week 20 <sup>‡</sup>	127	140	154
Week 24 <sup>‡</sup>	155	168	186*
OLE Week 24 <sup>†#</sup>	1	1	1
OLE Week 28	15	28	42
OLE Week 32	43	56	70
OLE Week 36	71	84	98
OLE Week 40	99	112	126
OLE Week 44	127	140	154
OLE Week 48	155	168	182
OLE Week 52 <sup>†¶</sup>	183	196	210
OLE Week 56	211	224	238
OLE Week 60	239	252	266
OLE Week 64	267	280	294
OLE Week 68	295	308	322
OLE Week 72	323	336	350
OLE Week 76	351	364	378

## **Table 1 Analysis Timepoints and Windows (cont.)**

OLE=Open-Label Extension.

<sup>‡</sup>Analysis timepoints during the parent studies are calculated using the date of randomization as the reference point. The analysis timepoints and windows for the parent studies are copied from the SAP for the parent studies.

<sup>#</sup> The following tests/assessments will not be necessary to collect at the start of OLE Week 24 visit because they are collected at Week 24 of the pivotal studies: nasal endoscopy, SNOT-22, EQ-5D-5L, AQLQ, UPSIT, PK, hematology, chemistry, and limited physical examination.

<sup>\*</sup> The last day of the Week 24 interval is 4 days longer to minimize missing data at the Week 24 timepoint. In addition, the last study day for the parent study is the minimum of Day 186 and the last day when the eDiary data was collected in the parent studies.

<sup>†</sup> The first dose of omalizumab in the OLE study is given during OLE Week 24 visit. The first day of OLE dosing is the new reference point for calculating study days in the OLE study. MOS Sleep Scale and Healthy Days Core Module are collected during OLE Week 24 visit.

<sup>¶</sup> The treatment-free follow-up period starts on Week 52.

### **4.3 ANALYSIS OF STUDY CONDUCT**

Descriptive statistics will be used to evaluate the conduct of this study. The number of patients enrolled will be tabulated by country, study site, and treatment assigned at randomization of the previous studies. Patient disposition, the number of patients enrolled, the number and percentage of patients received at least one dose of study drug, completing treatment, the treatment period and the follow-up period, and, the number and percentage of patients who undergo premature study drug discontinuation and study discontinuation (treatment period and/or follow-up period), as well as the reasons for discontinuations, will be tabulated by treatment received in the parent studies by cohort and pooled across cohorts.

### **4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY**

Demographic and baseline characteristics, including but not limited to age, sex, race/ethnicity, NPS, NCS, loss of sense of smell, ARS, PRS, TNSS, UPSIT, and SNOT-22 will be summarized at the baseline at randomization with descriptive statistics by treatment received in the parent study by cohort and pooled across cohorts. Baseline characteristics will be summarized by treatment received in the parent studies by cohort and pooled across cohorts, using mean, standard deviation, median, and range for continuous variables and number and percentages of patients for categorical variables, as appropriate.

### **4.5 EFFICACY ANALYSIS**

#### **4.5.1 Primary Efficacy Endpoint**

Primary efficacy analysis will be descriptive in nature; no formal hypothesis testing will be performed.

##### **4.5.1.1 Nasal Polyp Score**

Polyp size in each nasal passage will be graded through an assessment of the video nasal endoscopy (0–4 integer scale, see Appendix 3 of the Protocol) by a central panel

of independent sinus surgeons who are blinded to treatment assignment in the parent studies. NPS is the sum of the polyp scores in both nostrils (maximum score of 8). For patients who have had a relatively common surgical procedure called middle turbinectomy, scoring will be modified (see Appendix 3 of the Protocol). Nasal polyp scores will be assessed during OLE Weeks 36, 52, 64 and 76 visits. The change from baseline at each timepoint in NPS for each patient is defined as the NPS assessment assigned to the analysis timepoint (Table 1) minus the NPS at the randomization baseline.

#### **4.5.1.1.1 Primary Analysis**

To evaluate the sustained efficacy following continuation of treatment with omalizumab after an initial 24-week treatment period during the OLE and the duration of response following treatment discontinuation, change from baseline in NPS will be summarized at each timepoint (Weeks 4, 8, 16, and 24, and, OLE Weeks 36 and 52, along with OLE Weeks 64 and 76) for the FAS-OLE population using descriptive statistics based on the observed data (i.e., number of patients with available data, mean, median, standard deviation, and 95% CIs) by assigned treatment group by cohort and pooled across cohorts.

Both efficacy and durability of response will be assessed descriptively and graphically for the FAS-OLE population. No imputation will be applied to patients who received rescue treatment (nasal polypectomy or systemic corticosteroid), or, who discontinue study drug early due to progressive disease, adverse event, or lack of efficacy; observed data will be used for both parent studies and the OLE study. Worst observed post-baseline imputation will not be implemented due to the low occurrence of such events in the parent studies.

#### **4.5.1.1.2 Secondary Analysis**

The impact of longer treatment duration on durability of response according to NPS will be assessed separately using a mixed-effect model repeated measurement (MMRM) model for NPS. For the by-cohort analyses, the models will use change from baseline as the dependent variable, adjusted by geographic region through the use of a categorical variable and by baseline asthma comorbidity and aspirin sensitivity status, as well as timepoint (Weeks 4, 8, 16, and 24, and, OLE Weeks 36, 52, 64, and 76), Study GA39688/GA39855 baseline NPS, assigned treatment from parent studies, treatment by timepoint interaction, and Study GA39688/GA39855 baseline NPS by timepoint interaction. For the pooled analysis, an additional independent variable, study (a categorical variable) will be included in the model. Point estimates, 95% CIs, and p-values for the treatment effect (omalizumab vs. placebo) on change from baseline in NPS will be calculated on the basis of the model for all modeled timepoints, including OLE Week 76, using appropriate contrasts. Timepoints with fewer than 60 patients with available data per treatment group in the pooled population will be excluded from the by-cohort and pooled analyses.

For the by-cohort analyses, if issues with convergence arise in one or two cohorts, the unstructured covariance assumption will be replaced with a heterogeneous compound symmetry covariance assumption for both cohorts. If convergence issues still persist, analysis of covariance ANCOVA at each timepoint will be implemented for both cohorts. For the pooled analysis, if issues with convergence arise, the unstructured covariance assumption will be replaced with a heterogeneous compound symmetry covariance assumption and later ANCOVA at each timepoint if issues persist.

All missing data will be assumed as missing-at-random (MAR). No imputation will be applied to patients, who received rescue treatment (nasal polypectomy or systemic corticosteroid), or, who discontinued study drug early due to progressive disease, adverse event, or lack of efficacy; observed data will be used for both parent studies and the OLE study. Worst observed post-baseline imputation will not be implemented due to the low occurrence of such events in the parent studies.

#### **4.5.1.2 Nasal Congestion Score**

NCS is scored by patient on a 0–4 scale, with 0=not at all, 1=mild, 2=moderate, and 3=severe (see Appendix 4 of the protocol) every morning through OLE Week 76 via an eDiary. The calculation for daily NCS scores based the 7-day prior average follows the methods described in the parent studies' SAP. The change from baseline at each timepoint in NCS for each patient is defined as the NCS assessment assigned to the analysis timepoint ([Table 1](#)) minus the NCS at the randomization baseline.

##### **4.5.1.2.1 Primary Analysis**

To evaluate the sustained efficacy following continuation of treatment with omalizumab after an initial 24-week treatment period during the OLE and the duration of response following treatment discontinuation, change from baseline in NCS will be summarized at each timepoint (Weeks 4, 8, 12, 16, 20 and 24, and, OLE Weeks 28, 32, 36, 40, 44, 48, and 52, along with OLE Weeks 56, 60, 64, 68, 72, and 76) for the FAS-OLE population using descriptive statistics based on the observed data (i.e., number of patients with available data, mean, median, standard deviation, and 95% CIs) by assigned treatment group by cohort and pooled across cohorts.

Both efficacy and durability of response will be assessed descriptively and graphically for the FAS-OLE population. No imputation will be applied to patients, who received rescue treatment (nasal polypectomy or systemic corticosteroid), or, who discontinued study drug early due to progressive disease, adverse event, or lack of efficacy; observed data will be used for both parent studies and the OLE study. Worst observed post-baseline imputation will not be implemented due to the low occurrence of such events in the parent studies.

##### **4.5.1.2.2 Secondary Analysis**

The impact of longer treatment duration on durability of response according to NCS will be assessed separately using a mixed-effect model repeated measurement (MMRM)

model for NCS. For the by-cohort analyses, the models will use change from baseline as the dependent variable, adjusted by geographic region through the use of a categorical variable and by baseline asthma comorbidity and aspirin sensitivity status, as well as timepoint (Weeks 4, 8, 12, 16, 20 and 24, and, OLE Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72 and 76), Study GA39688/GA39855 baseline NCS, assigned treatment from parent studies, treatment by timepoint interaction, and Study GA39688/GA39855 baseline NCS by timepoint interaction. For the pooled analysis, an additional independent variable, study (a categorical variable) will be included in the model. Point estimates, 95% CIs, and p-values for the treatment effect (omalizumab vs. placebo) on change from baseline in NCS will be calculated on the basis of the model for all modeled timepoints, including Week 76, using appropriate contrasts. Timepoints with fewer than 60 patients with available data per treatment group in the pooled population will be excluded from the by-cohort and pooled analyses.

For the by-cohort analyses, if issues with convergence arise in one or two cohorts, the unstructured covariance assumption will be replaced with a heterogeneous compound symmetry covariance assumption for both cohorts. If convergence issues still persist, analysis of covariance ANCOVA at each timepoint will be implemented for both cohorts. For the pooled analysis, if issues with convergence arise, the unstructured covariance assumption will be replaced with a heterogeneous compound symmetry covariance assumption and later ANCOVA at each timepoint if issues persist.

All missing data will be assumed as missing-at-random (MAR). No imputation will be applied to patients, who received rescue treatment (nasal polypectomy or systemic corticosteroid), or, who discontinued study drug early due to progressive disease, adverse event, or lack of efficacy; observed data will be used for both parent Studies and the OLE study. Worst observed post-baseline imputation will not be implemented due to the low occurrence of such events in the parent studies.

## **4.5.2            Secondary Efficacy Endpoints**

### **4.5.2.1        Nasal Symptoms**

Nasal symptoms other than NCS (i.e., TNSS, loss of sense of smell, posterior rhinorrhea, and anterior rhinorrhea) will be analyzed according to the same methods as those used for NCS score specified in Section 4.5.1.2.2 and using separate MMRM models as specified above. This analysis will only be performed on the pooled population across cohorts according to the treatment assigned (omalizumab or placebo) at randomization in the parent studies. Timepoints with fewer than 60 patients with available data per treatment group in the pooled population will be excluded from the pooled analysis.

### **4.5.2.2        SNOT-22, UPSIT, EQ-5D-5L and AQLQ**

SNOT-22 and UPSIT will be analyzed according to the same methods as those used for NPS as specified in Section 4.5.1.2.2 and using separate MMRM models as specified above. The model will include Weeks 4 (SNOT-22 only), 8, 16, and 24 and OLE Weeks 36, 52, 64 and 76. This analysis will only be performed on the pooled population across

cohorts according to the treatment assigned (omalizumab or placebo) at randomization in the parent studies. Timepoints with fewer than 60 patients with available data per treatment group in the pooled population will be excluded from the pooled analysis

Change from baseline (at randomization) in EQ-5D-5L and AQLQ, will be summarized at each timepoint (Weeks 4 [AQLQ only], 8 [AQLQ only], 16 and 24, and, OLE Weeks 36, 52, 64 and 76) for the FAS-OLE population using descriptive statistics based on the observed data (i.e., number of patients with available data, mean, median, min, max, and interquartile range) by assigned treatment group by cohort and pooled across cohorts.

#### **4.5.3            Exploratory Efficacy Endpoints**

##### **4.5.3.1        Reduction in the need for surgery by OLE Weeks 36 and 52**

A reduction in the need for surgery by OLE Weeks 36 and 52 is defined as by an NPS of  $\leq 4$  (unilateral score of  $\leq 2$  on each side) for patients who had an NPS of  $\geq 5$  at start of parent study, along with an improvement in SNOT-22 score of  $\geq 8.9$  at OLE Weeks 36 or Weeks 52, without requiring rescue treatment (systemic corticosteroid or surgery) any time in between. Patients without valid Weeks 36 or 52 assessment will have a missing outcome for the time point of interest.

Patients, who have rescue treatment any time (during parent studies or OLE) prior to OLE Weeks 36 or 52, or, who discontinue study drug due to progressive disease, adverse event, or lack of efficacy will be counted as no reduction in the need for surgery was achieved.

This analysis will be descriptive in nature showing only the number and percentages of patients who achieve reduction in the need for surgery by treatment assigned pooled across cohorts.

##### **4.5.3.2        Requirement of rescue treatment or having had surgery for nasal polyps through OLE Week 52**

Patients who discontinue study drug due to progressive disease, adverse event, or lack of efficacy any time (during parent studies or OLE) through OLE Week 52 will be counted as requiring rescue treatment and having had surgery. Patients experience multiple events (rescue treatment, surgery or discontinuation of study drug due to due to progressive disease, adverse event, or lack of efficacy) will be counted only once per patient. Patients who discontinue early prior to OLE Week 52 but do not experience events or intercurrent events will be imputed as missing.

This analysis will be descriptive in nature showing only the number and percentages of patients require rescue treatment and surgery by treatment assigned pooled across cohorts.

#### **4.5.3.3 Requirement of rescue treatment through OLE Week 52**

Patients who discontinue the study drug due to progressive disease, adverse event, or lack of efficacy any time (during parent studies or OLE) through OLE Week 52 will be counted as requiring rescue treatment. Patients experience multiple events (rescue treatment or discontinuation of study drug due to progressive disease, adverse event, or lack of efficacy) will be counted only once per patient. Patients who discontinue early prior to OLE Week 52 but do not experience events or intercurrent events will be imputed as missing.

This analysis will be descriptive in nature showing only the number and percentages of patients require rescue treatment by treatment assigned pooled across cohorts.

#### **4.5.3.4 Having had surgery for nasal polyps through OLE Week 52**

Patients who discontinue study drug due to progressive disease, adverse event, or lack of efficacy any time (during parent studies or OLE) through OLE Week 52 will be counted as requiring surgery. Patients experience multiple events (surgery or discontinuation of study drug due to progressive disease, adverse event, or lack of efficacy) will be counted only once per patient. Patients who discontinue early prior to OLE Week 52 but do not experience events or intercurrent events will be imputed as missing.

This analysis will be descriptive in nature showing only the number and percentages of patients require surgery by treatment assigned pooled across cohorts.

#### **4.5.3.5 Change from Week 24 in MOS Sleep Scale**

The MOS Sleep Scale is a 12-item questionnaire asking patients to rate various dimensions of their sleep over the past 4 weeks. Several scores can be derived: sleep disturbance, snoring, shortness of breath, sleep adequacy, somnolence, Sleep Problems Index I, Sleep Problems Index II, sleep quantity, and optimal sleep. Derivation of the sleep scores will use the algorithms described in Version 1.0 of the MOS Sleep Scale scoring manual ([Spritzer and Hays 2003](#)).

Changes from OLE enrollment (Weeks 24) by visit (Weeks 36, 52, 64 and 76) will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) for patients who were randomized to receive placebo in the parent studies. Patients with missing data will be excluded from this analysis.

#### **4.5.3.6 Change from Week 24 in Healthy Days Core Module**

The Healthy Days Core Module is a four-item questionnaire that asks patients to rate their overall health and number of healthy days they experienced in the past month. It is a brief assessment of the overall physical and mental health of a patient. Derivation of the self-rated health, physically unhealthy days, mentally unhealthy days, activity limitation days, unhealthy days and percent with frequent mental distress will use the algorithms described in scoring methods ([CDC](#)).



Changes from OLE enrollment (Weeks 24) by visit (Weeks 36, 52, 64 and 76) will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) for patients who were randomized to receive placebo in the parent studies. Patients with missing data will be excluded from this analysis.

#### **4.5.4            Exploratory Psychometric Objective**

##### **4.5.4.1        Patient Global Impression of Change**

The Patient Global Impression of Change is a single-item assessment of the patient's impression of his or her change in nasal polyp symptoms since the previous study visit.

Answers to this questionnaire will be summarized by visit (Weeks 36, 52, 64 and 76) and by number percentage of patients endorsing each category (Very much better, Much better, etc.) for patients who were randomized to receive placebo in the parent studies. In addition, the proportion of patients who reported improvement (very much better, much better, and a little better), no change, or worsening (a little worse, much worse, and very much worse) will be summarized by visit. Patients with missing data will be excluded from this analysis.

#### **4.6                PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES**

Predose serum omalizumab concentrations ( $C_{min}$ ) and total and free IgE will be measured at OLE Week 36 and Week 52 during the treatment period and at OLE Weeks 64 and 76 during the follow-up period according to the summary of activities (Protocol WA40169 Appendix 1). These concentrations will be summarized using descriptive statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum) by timepoint based on the safety analysis population.

#### **4.7                SAFETY ANALYSES**

##### **4.7.1            Exposure of Study Medication**

In this study, patient weights and IgE values used to determine study drug dosing will be based only on values from the screening period of the parent studies. (see Section 4.1.3 of the Protocol for further details). Omalizumab will be dosed according to the same dosing table used in the parent studies. The number and percentage of patients receiving each dose of the study drug will be summarized by assigned treatment pooled across the parent studies and overall. The overall duration of exposure (weeks), and the number of doses received will be summarized by descriptive statistics (mean, SD, median, range). The overall duration of exposure will be summarized by number of patients and percentage categories (i.e., 0–4 weeks, >4–8 weeks, >8–12 weeks, etc.) Duration of treatment will be defined based on the difference (in days) between the dates of the first and last dose of study drug plus 1 day. Two summaries of exposure will be produced: counting from the first dose in the parent studies and counting from the first dose of the OLE study.

#### **4.7.2      Adverse Events**

Verbatim descriptions of treatment-emergent adverse events (TEAEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as any new AE or any worsening of an existing condition with an onset after the first study drug administration in the OLE study. Summaries of treatment-emergent events will be provided for each of the following categories:

- All AEs
- All AEs by severity
- AEs assessed as related to study drug by the investigator
- SAEs
- AEs leading to discontinuation of study drug
- Adverse events of special interest (AESI) (i.e., anaphylaxis/anaphylactoid reactions, drug induced liver injury, and suspected transmission of an infectious agent by the study drug)
- Deaths

In addition, all AEs, SAEs and AEs leading to discontinuation of study drug will be summarized to compare patients who received omalizumab doses higher than the approved asthma-dosing table (doses  $\geq$  450 mg) versus approved doses (doses  $\leq$  375 mg)

Treatment-emergent adverse events are defined as any new adverse events or any worsening of an existing conditions with an onset date on or after the first study drug administration date in the OLE study.

Non-treatment emergent adverse events include all adverse events that are not treatment emergent in the OLE study. Non-treatment emergent adverse events will be listed.

Treatment-emergent adverse events with onset during open label treatment are defined as any new AEs or any worsening of an existing condition with an onset date on or after the first study drug administration date and occurring prior to 29 days after the last dose of omalizumab in the OLE study. Treatment-emergent adverse events with onset during follow up are defined as any new AEs or any worsening of an existing condition with an onset date on or after the first study drug administration date and occurring on or after 29 days after the last dose of omalizumab in the OLE study.

The AESIs will be identified as defined below. Summaries by treatment arm will include tabulations by MedDRA preferred terms and/or listings, as appropriate.

- Anaphylactic, anaphylactoid, and hypersensitivity reactions: Potential cases of anaphylactic, anaphylactoid, and hypersensitivity reactions will be identified and

sent for adjudication by an independent AAC (see Section 3.2.1). Members of the AAC review blinded data to adjudicate cases as anaphylaxis per Sampson's Criteria and for relatedness to study drug. A detailed description of the process for identification of potential events and data flow is provided in the AAC Charter. Events adjudicated by the AAC as meeting Sampson's Criteria for anaphylaxis and relatedness to study drug will be summarized. Additionally, a listing of all possible cases of anaphylaxis will be produced.

- Suspected transmission of an infectious agent by the study drug: Events will be identified using the Preferred Term (PT) "Suspected transmission of an infectious agent via product".
- Drug-induced liver injury: Events will be identified and summarized if any one of the following three criteria are met: 1) treatment-emergent aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $> 3 \times$  upper limit of normal (ULN) in combination with total bilirubin  $> 2 \times$  ULN; 2) treatment-emergent AST or ALT  $> 3 \times$  ULN in combination with clinical jaundice as represented by any one of the following preferred terms: ocular icterus, jaundice acholuric, jaundice hepatocellular; or 3) if the patient is reported to have the preferred term drug-induced liver injury.

The following AEs identified as risks associated with omalizumab will be listed and summarized separately:

- Serum Sickness Syndrome/Serum Sickness Like Disease (SSLD) (PTs "Serum sickness" and "Serum sickness-like reaction")
- Antibody formation to omalizumab (PTs "Drug specific antibody present", "Human anti-human antibody test", and "Drug specific antibody")
- The following AEs identified as risks associated with omalizumab will be first identified according to the broad search criteria below. Events will be evaluated by a Sponsor scientist and only confirmed events will be summarized. Events identified by the broad search will be listed with the events confirmed by the sponsor scientist flagged:
  - Churg Strauss Syndrome (CSS)/Hyper Eosinophilic Syndrome (HES)/Eosinophilic Granulomatosis with Polyangiitis (EGPA) (broad search criteria: HLGT "Vascular inflammations" and HLT "Eosinophilic disorders")
  - Thrombocytopenia (SMQ [Standardized MedDRA Query] "Haematopoietic thrombocytopenia" [Broad] and PT "Immune thrombocytopenic purpura" [ITP]).
  - Arterial Thrombotic Events (ATEs) (SMQs [broad]: "Myocardial Infarction" and "Other ischaemic heart disease", SMQs [narrow]: "Ischaemic central nervous system vascular conditions", "Haemorrhagic central nervous system vascular conditions" and PTs "Hemiparesis", "Hemiplegia", "Sudden cardiac death", "Sudden death", and "Cardiac death").

- Malignant neoplasms (SMQ “Malignancies” [broad])
- Parasitic infections (broad search criteria: the MedDRA High Level Group Terms (HGLT) of “Helminthic disorders”, “Mycobacterial infectious disorders”, and “Protozoal infectious disorders”, MedDRA High Level Term (HLT) of “Listeria infections”)

### **4.7.3      Laboratory Data**

Serum chemistry and hematology values and changes from the baseline at randomization in clinical laboratory values will be summarized by descriptive statistics (mean, SD, median, minimum, maximum) by treatment received over the course of the studies (parent studies and OLE). The worst post-baseline (OLE-enrollment) World Health Organization (WHO) grade for clinical laboratory values collected during the OLE study will be summarized by treatment received pooled across the parent studies for platelets, hemoglobin, neutrophils, creatinine, ALT, AST, total bilirubin, alkaline phosphatase, sodium, and potassium. Worst post-baseline (OLE-enrollment) FDA Healthy Volunteers grade for clinical laboratory values of eosinophils and white blood cells will be presented by treatment received pooled across the parent studies.

Shift tables of highest WHO grade post-baseline by baseline (OLE-enrollment) grade for platelets, AST, ALT, and total bilirubin will be presented by treatment received pooled across the parent studies

Anti-drug-body will be summarized by timepoint and treatment received pooled across the parent studies.

### **4.7.4      Vital Signs**

Vital signs (pulse rate, systolic and diastolic blood pressure while the patient is in a seated position) and changes from baseline (randomization) will be summarized over the course of the studies (parent studies and OLE) by descriptive statistics (mean, SD, median, minimum, and maximum) by treatment assigned pooled across the parent studies.

## **4.8              MISSING DATA**

Rules for handling missing data are specific to the endpoints and details are given within the efficacy Section 4.5 and safety Section 4.7.

## **4.9              INTERIM ANALYSES**

No efficacy interim analyses are planned for this study. Two interim safety analyses have been conducted in support of marketing application to Health Authorities for the CRSwNP indication. Details for the two interim analyses are published in the Interim Statistical Analysis Plan.

## **5.           REFERENCES**

CDC: Available at <https://www.cdc.gov/hrqol/methods.htm>

FDA 2006: Available at <https://www.fda.gov › regulatoryinformation › guidances › ucm127073>

Spritzer KL, Hays RD. MOS sleep scale: a manual for use and scoring, version 1.0. Los Angeles, CA: RAND, 2003.

## Appendix 1 Protocol Synopsis

**TITLE:** OPEN-LABEL EXTENSION STUDY OF OMALIZUMAB IN PATIENTS WITH CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

**PROTOCOL NUMBER:** WA40169

**VERSION NUMBER:** 1

**EUDRACT NUMBER:** 2017-003450-16

**IND NUMBER:** 5369

**TEST PRODUCT:** Omalizumab (IGE025)

**PHASE:** 3

**INDICATION:** Chronic rhinosinusitis with nasal polyps

**SPONSOR:** F. Hoffmann-La Roche Ltd

### **Objectives and Endpoints**

The overall purpose of this study is to evaluate the safety, efficacy, and durability of response of omalizumab in an open-label setting in adult patients with chronic rhinosinusitis with nasal polyps (CRSwNP) who completed the double-blind placebo-controlled Phase III Study GA39688 or GA39855. Specific objectives and corresponding endpoints for the study are outlined below.

<b>Primary Safety Objective</b>	<b>Corresponding Endpoints</b>
<ul style="list-style-type: none"> <li>To evaluate adverse events associated with usage of omalizumab in patients with CRSwNP</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of serious and non-serious adverse events</li> <li>Incidence of adverse events leading to omalizumab discontinuation</li> </ul>
<b>Secondary Safety Objective</b>	<b>Corresponding Endpoint</b>
<ul style="list-style-type: none"> <li>To evaluate any potential laboratory abnormalities associated with usage of omalizumab in patients with CRSwNP</li> </ul>	<ul style="list-style-type: none"> <li>Clinically significant change in laboratory values</li> </ul>
<b>Primary Efficacy Objective</b>	<b>Corresponding Endpoints <sup>a</sup></b>
<ul style="list-style-type: none"> <li>To evaluate efficacy of continued treatment with omalizumab after an initial 24-week treatment period</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline at Weeks 4<sup>b</sup>, 8<sup>b</sup>, 16<sup>b</sup>, 24<sup>b</sup>, 36, and 52 in NPS</li> <li>Change from baseline at Weeks 4<sup>b</sup>, 8<sup>b</sup>, 12<sup>b</sup>, 16<sup>b</sup>, 20<sup>b</sup>, 24<sup>b</sup>, 28, 32, 36, 40, 44, 48, and 52 in NCS</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the durability of response following treatment discontinuation</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline at Weeks 52, 64, and 76 in NPS</li> <li>Change from baseline at Weeks 52, 56, 60, 64, 68, 72, and 76 in NCS</li> </ul>

Secondary Efficacy Objectives	Corresponding Endpoints <sup>a</sup>
<ul style="list-style-type: none"> <li>• To evaluate the impact of treatment duration with omalizumab on durability of response</li> </ul>	<ul style="list-style-type: none"> <li>• Change from baseline at Week 76 in the following assessments: <ul style="list-style-type: none"> <li>– NPS</li> <li>– NCS</li> <li>– TNSS</li> <li>– Loss of smell</li> <li>– Posterior rhinorrhea</li> <li>– Anterior rhinorrhea</li> <li>– SNOT-22</li> <li>– EQ-5D-5L</li> <li>– AQLQ (patients with comorbid asthma only)</li> <li>– UPSIT</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• To evaluate efficacy of continued treatment with omalizumab after an initial 24-week treatment period</li> </ul>	<ul style="list-style-type: none"> <li>• Change from baseline at Weeks 4 <sup>b</sup>, 8 <sup>b</sup>, 12 <sup>b</sup>, 16 <sup>b</sup>, 20 <sup>b</sup>, 24 <sup>b</sup>, 28, 32, 36, 40, 44, 48, and 52 in the following assessments: <ul style="list-style-type: none"> <li>– TNSS</li> <li>– Posterior rhinorrhea</li> <li>– Anterior rhinorrhea</li> <li>– Loss of smell</li> </ul> </li> <li>• Change from baseline at Weeks 4 <sup>b</sup>, 8 <sup>b</sup>, 16 <sup>b</sup>, 24 <sup>b</sup>, 36, and 52 in the following assessments: <ul style="list-style-type: none"> <li>– SNOT-22</li> <li>– AQLQ (patients with comorbid asthma only)</li> </ul> </li> <li>• Change from baseline at Weeks 16 <sup>b</sup>, 24 <sup>b</sup>, 36, and 52 in EQ-5D-5L</li> <li>• Change from baseline at Weeks 8 <sup>b</sup>, 16 <sup>b</sup>, 24 <sup>b</sup>, 36, and 52 in UPSIT</li> </ul>

<b>Secondary Efficacy Objectives (cont.)</b>	<b>Corresponding Endpoints <sup>a</sup> (cont.)</b>
<ul style="list-style-type: none"> <li>To evaluate the durability of response following treatment discontinuation</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline at Weeks 52, 56, 60, 64, 68, 72, and 76 in the following assessments: <ul style="list-style-type: none"> <li>TNSS</li> <li>Posterior rhinorrhea</li> <li>Anterior rhinorrhea</li> <li>Loss of smell</li> </ul> </li> <li>Change from baseline at Weeks 64 and 76 in SNOT-22</li> <li>Change from baseline at Weeks 52, 64, and 76 in the following assessments: <ul style="list-style-type: none"> <li>EQ-5D-5L</li> <li>AQLQ (in patients with comorbid asthma only)</li> <li>UPSIT</li> </ul> </li> </ul>
<b>Exploratory Efficacy Objectives</b>	<b>Corresponding Endpoints</b>
<ul style="list-style-type: none"> <li>To evaluate efficacy of continued treatment with omalizumab after an initial 24-week treatment period</li> </ul>	<ul style="list-style-type: none"> <li>Reduction in the need for surgery by Weeks 36 and 52, as defined by an NPS of <math>\leq 4</math> (unilateral score of <math>\leq 2</math> on each side) and improvement in SNOT-22 score of <math>\geq 8.9</math></li> <li>Requirement of rescue treatment (systemic CS for <math>\geq 3</math> consecutive days) or having had surgery for nasal polyps through Week 52</li> <li>Requirement of rescue treatment (systemic CS for <math>\geq 3</math> consecutive days) through Week 52</li> <li>Having had surgery for nasal polyps through Week 52</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the effect of omalizumab on sleep quality after an initial 24-week treatment period of placebo</li> </ul>	<ul style="list-style-type: none"> <li>Change from Week 24 at Weeks 36, 52, 64, and 76 in MOS Sleep Scale</li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the effect of omalizumab on overall physical and mental health after an initial 24-week treatment period of placebo</li> </ul>	<ul style="list-style-type: none"> <li>Change from Week 24 at Weeks 36, 52, 64, and 76 in Healthy Days Core Module</li> </ul>
<b>Exploratory Psychometric Objective</b>	<b>Corresponding Endpoint</b>
<ul style="list-style-type: none"> <li>To collect data to support psychometric analyses to assess sensitivity of EQ-5D-5L</li> </ul>	<ul style="list-style-type: none"> <li>PGIC at Weeks 36, 52, 64, and 76</li> </ul>

AQLQ = Asthma Quality of Life Questionnaire; CRSwNP = chronic rhinosinusitis with nasal polyps; EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire; MOS = Medical Outcomes Study; NCS = nasal blockage/congestion score; NPS = nasal polyp score; PGIC = Patient Global Impression of Change; SNOT-22 = Sino-Nasal Outcome Test-22; TNSS = total nasal symptom score; UPSIT = University of Pennsylvania Smell Identification Test.

<sup>a</sup> Baseline is defined as the last pre-treatment measurement prior to randomization in Studies GA39688/GA39855 (i.e., baseline of Studies GA39688/GA39855).

<sup>b</sup> These data are from Studies GA39688/GA39855.



## **Study Design**

### **Description of Study**

This study is an open-label clinical study. Patients who have completed the treatment period of Study GA39688/GA39855 and fulfill the eligibility criteria for the open-label extension (OLE) study will be enrolled.

Patients will be eligible for enrollment in the study at the Week 24 visit of Study GA39688/GA39855 or within 28 days after the Week 24 visit of Study GA39688/GA39855. Whenever possible, patients should enroll and begin open-label dosing of omalizumab at the Week 24 visit of Study GA39688/GA39855 rather than return for a subsequent visit. However, if necessary, patients may return within 28 days of the Week 24 visit of Study GA39688/GA39855 to enroll and begin dosing. The rationale for enrolling patients into this OLE study at the Week 24 visit of Study GA39688/GA39855, or within a short period of time thereafter, is to allow for relatively continuous exposure to omalizumab over a 52-week period of time. Enrollment at the Week 24 visit of Study GA39688/GA39855 may also reduce patient burden by obviating the need for an additional clinic visit.

Informed consent into this OLE study must be completed by the time of enrollment and open-label omalizumab dosing. Whenever possible, investigators should begin the consent process for this OLE study well in advance of the Week 24 visit of Study GA39688/GA39855. Providing information about this OLE study to patients early in Study GA39688/GA39855 will facilitate a seamless transition into this protocol.

After enrollment into this OLE study, patients will receive 28 weeks of dosing of open-label omalizumab before entering a 24-week off-treatment observation phase of the study. In this protocol, the timing of the visit schedule for this OLE study is defined in time relative to the baseline of Study GA39688/GA39855. That is, the first visit of this OLE study is referred to as the "Week 24 Visit." Similarly, the last visit occurring during the 28-week treatment phase is referred to as the "Week 52 Visit," and the final visit of the 24-week follow-up period is referred to as the "Week 76 Visit." Note that the Week 52 Visit is not only considered to be the last visit of the treatment phase, but also the first visit of the follow-up period.

The first dose of open-label omalizumab should be administered on the day of enrollment into this OLE study ("Week 24 Visit"). The dosing table will be the same as that used with Study GA39688/GA39855.

Patients should remain on stable doses of intranasal corticosteroid (CS) therapy (mometasone nasal spray 200 µg twice a day [BID]) for the entire treatment and follow-up periods. That is, patients should remain on stable doses of intranasal CS therapy for both the treatment period of Study GA39688/GA39855, the treatment period of this current study, and the follow-up period of this current study. As in Study GA39688/GA39855, patients deemed by the investigator to be intolerant to a BID regimen of mometasone may remain on a stable dosage of mometasone once daily (QD) (two sprays/nostril, both nostrils, 50 µg/spray QD for a total daily dosage of 200 µg). Any patient transitioned to daily mometasone should remain on this regimen for the remainder of the study.

Safety, efficacy, and patient-reported outcome (PRO) measures will be assessed during the treatment and follow-up periods, as detailed in the schedule of activities.

After the treatment period ends (after Week 52 Visit), patients will be followed for an additional 24 weeks as part of the follow-up period. There is no dose administered at Week 52. During the follow-up period, patients will be asked to continue completion of their daily electronic diary (eDiary) assessment of nasal symptoms. An important objective of this portion of this study will be to understand the extent and timing of any relapse in symptoms related to nasal polyposis. Patients will return to clinic at Week 64 and for a final visit at Week 76, with telephone visits at Weeks 56, 60, 68, and 72.

All patients who discontinue study drug early during the treatment period will be asked to complete the remainder of the treatment period and then complete the 24-week follow-up period. For example, if a patient discontinues study drug at Week 32, that patient would be asked to return for the Week 36 and Week 52 visits to complete all assessments and would then complete the follow-up visits.

Nasal polyp score (NPS) will be assessed by video nasal endoscopy, scored using a standard scoring system (maximum NPS is 8) by a central panel of independent sinus surgeons who are

blinded to treatment assignment from Studies GA39688/GA39855 and blinded to timepoint of assessment within this OLE study (e.g., readers will not know whether nasal endoscopy was obtained during the treatment period or the follow-up period).

### **Number of Patients**

All subjects completing Week 24 of Study GA39688/GA39855 and otherwise meeting inclusion and exclusion criteria are eligible to enroll. It is anticipated that a maximum of approximately 240 patients will enroll into this study.

### **Target Population**

#### Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–75 years old, inclusive, at time of signing informed consent form for Study GA39688 or Study GA39855
- Ability to comply with the study protocol, in the investigator's judgment
- Participation in Study GA39688 or Study GA39855, including completion of endoscopy and other assessments at Week 24, without discontinuation of study drug
- Completion of eDiary daily assessments for at least 4 out of 7 days in the week prior to the Week 24 visit of Study GA39688 or Study GA39855
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the treatment period and for 60 days after the last dose of study drug
  - Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
  - Acceptable methods of contraception include surgical sterilization (e.g., bilateral tubal ligation, vasectomized partner), hormonal contraception (e.g., implantable, injectable, patch, oral), and intrauterine device (IUD).
  - Women of childbearing potential must have a negative pregnancy test result prior to initiation of study drug in this study.

#### Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Anaphylaxis/hypersensitivity related to study drug in Study GA39688/GA39855
- Serious adverse events related to study drug in Study GA39688/GA39855 that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Uncontrolled epistaxis within Study GA39688 or GA39855
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the last dose of omalizumab
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

### **End of Study and Length of Study**

The end of the study is defined as the date of the last patient's last visit (LPLV). The LPLV is expected to occur approximately 52 weeks after the last patient is enrolled (28-week treatment period of OLE followed by 24-week follow-up period).

### **Investigational Medicinal Products**

The investigational medicinal product (IMP) for this study is omalizumab.

**Test Product (Investigational Drug)**

Study drug (omalizumab) will be administered subcutaneously to patients using a disposable 25-gauge needle in the deltoid region of the right or left arm. Alternatively, the injections can be administered in the thigh, if medically significant reasons preclude administration in the deltoid region.

Omalizumab will be administered subcutaneously every 2 or 4 weeks. Because the solution is slightly viscous, the injection may take 5–10 seconds to administer. The dose (mg) and dosing frequency will be determined by serum total IgE level (IU/mL) (measured before the start of treatment via central laboratory) and body weight (kg). Assignment of omalizumab dose will be determined by using the study drug–dosing table. Doses of > 150 mg are divided among more than one injection site to limit injections to no more than 150 mg per site. The reconstituted vial is to be used for single-dose administration only.

**Non-Investigational Medicinal Products**

In this study, mometasone furoate monohydrate nasal spray is considered a non-IMP and is used as background therapy only.

**Statistical Methods****Primary Analysis**

The analysis of complete data from the study, including data from the safety follow-up period, will be performed when all patients have either discontinued the study early or completed the safety follow-up period, all data from the study are in the database, and the database is cleaned and locked.

**Determination of Sample Size**

No formal sample size calculation was performed for this study because the primary analysis is descriptive in nature, there will be no formal hypothesis testing, and this study is an OLE of previous studies (Studies GA39688 and GA39855), which plan to enroll approximately 240 patients in total (120 patients each). In order to be eligible for enrollment into this study, the patient must complete assessments at Week 24 in the prior study without discontinuation of study drug. Therefore, due to the inclusion criteria of this study and potential dropout from Studies GA39688 and GA39855, the sample size of approximately 240 patients is a maximum.

## Appendix 2 Schedule of Assessments

Assessments	Open-Label Treatment Period				Follow-Up Period					
	Start of OLE/Wk24	Wk 36	Wk 52	Wk 56 <sup>a</sup>	Wk 60 <sup>a</sup>	Wk 64	Wk 68 <sup>a</sup>	Wk 72 <sup>a</sup>	Wk 76	DT/ET <sup>b</sup>
Informed Consent	x									
Omaliuzumab treatment <sup>c</sup>	<----->									
NPS endoscopy <sup>d, e</sup>		x	x			x			x	x
Nasal symptoms (eDiary) <sup>f</sup>	<----->									
Nasal symptoms (interview) <sup>g</sup>	x	x	x	x	x	x	x	x	x	x
SNOT-22 <sup>d</sup>		x	x			x			x	x
EQ-5D-5L <sup>d</sup>		x	x			x			x	x
AQLQ <sup>d, h</sup>		x	x			x			x	x
UPSIT <sup>d</sup>		x	x			x			x	x
MOS Sleep Scale	x	x	x			x			x	x
Healthy Days Core Module	x	x	x			x			x	x
PGIC		x	x			x			x	x
PK <sup>d, i</sup>		x	x			x			x	x
ADA						x			x	x
Hematology <sup>d</sup>		x	x			x			x	x
Chemistry <sup>d</sup>		x	x			x			x	x
Total IgE <sup>i</sup>		x	x			x			x	x
Free IgE <sup>i</sup>		x	x			x			x	x
Urine pregnancy test <sup>j</sup>	x	x	x	x	x	x	x	x	x	x

## Appendix 2 Schedule of Assessments (cont.)

Assessments	Open-Label Treatment Period			Follow-Up Period						
	Start of OLE/Wk24	Wk 36	Wk 52	Wk 56 <sup>a</sup>	Wk 60 <sup>a</sup>	Wk 64	Wk 68 <sup>a</sup>	Wk 72 <sup>a</sup>	Wk 76	DT/ET <sup>b</sup>
Weight	x									
Limited physical examination <sup>d</sup>		x	x			x			x	x
Vital signs <sup>k</sup>	x	x	x			x			x	x
Adverse events <sup>l</sup>	<----->									
Concomitant medications <sup>l,m</sup>	<----->									

ADA=anti-drug antibody; AQLQ=Asthma Quality of Life Questionnaire; DT=dosing termination; eDiary=electronic diary; EQ-5D-5L=EuroQol 5-Dimension 5-Level Questionnaire; ET=early termination; MOS=Medical Outcomes Study; NPS = nasal polyp score; OLE=open-label extension; PGIC=Patient Global Impression of Change; PK=pharmacokinetic; PRO = patient-reported outcome; Q2W=every 2 weeks; Q4W=every 4 weeks; SNOT-22 = Sino-Nasal Outcome Test-22; UPSIT=University of Pennsylvania Smell Identification Test; Wk=week.

<sup>a</sup> Telephone visits take place at Weeks 56, 60, 68, and 72 to assess adverse events, concomitant medications, and telephone-based PROs.

<sup>b</sup> Patients who discontinue study drug or discontinue from the study will be asked to complete the DT/ET visit.

<sup>c</sup> Patients return to clinic every 2 or 4 weeks to receive open-label omalizumab. Last omalizumab dose is received at Week 48 for patients receiving Q4W dosing and at Week 50 for patients receiving Q2W dosing.

<sup>d</sup> The following tests/assessments will not be necessary to collect at start of OLE/Week 24 because they are collected at Week 24 of the pivotal studies: nasal endoscopy, SNOT-22, EQ-5D-5L, AQLQ, UPSIT, PK, hematology, chemistry, and limited physical examination. A full physical examination will not be necessary as part of this OLE study because of the full physical examination at the initiation of Study GA39688 and GA39855.

<sup>e</sup> If initial video endoscopy done during visit is of insufficient quality to allow for assessment of nasal polyps score, patient should return to clinic within 10 working days to repeat video endoscopy. Patients are expected to undergo a total of four endoscopies in this OLE study, except in situations in which video endoscopy needs to be repeated because of insufficient quality.

<sup>f</sup> Patients will be instructed to complete the questions in their eDiary in the morning, within approximately 1 hour of awakening. The same questions are assessed via eDiary during this OLE study as are being assessed during the treatment period of Study GA39688/GA39855.

<sup>g</sup> Nasal symptoms with a 7-day recall will be assessed in-clinic via in-person interview at Weeks 24, 36, 52, 64, and 76 and will be assessed via telephone interview at Weeks 56, 60, 68, and 72

## **Appendix 2**

### **Schedule of Assessments (cont.)**

- <sup>h</sup> AQLQ only in asthma patients
- <sup>i</sup> The Week 36 PK, total IgE, and free IgE collection should be conducted prior to the omalizumab dose.
- <sup>j</sup> Urine pregnancy testing should be conducted every 4 weeks during the treatment period at Weeks 24, 28, 32, 36, 40, 44, 48, and 52. Urine pregnancy test at Week 24 does not need to be repeated if performed at Week 24 as part of Study GA39688/GA39855 and if completed within 24 hours of study drug administration as part of the initial visit of this OLE study.
- <sup>k</sup> Vital signs collected at every visit (every 2 weeks in patients receiving omalizumab Q2W and every 4 weeks in patients receiving omalizumab Q4W).
- <sup>l</sup> Adverse events and concomitant medications should be assessed and recorded at least monthly.
- <sup>m</sup> Patients will remain on mometasone intranasally throughout the study as specified in Section 4.3.3 (of the protocol). At each visit the investigator must ensure that the patient has the necessary doses up to the next visit

## **Appendix 3**

### **Sampson's Criteria for Diagnosing Potential Cases of Anaphylaxis**

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

- 1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

**AND AT LEAST ONE OF THE FOLLOWING:**

- a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
  - b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
- 2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    - a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    - b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    - c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    - d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
  - 3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    - a) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Source: Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.