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

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PROTOCOL

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TABLE OF CONTENTS

PROTOCOL ACCEPTANCE FORM 9

PROTOCOL SYNOPSIS 10

1. BACKGROUND 18
   - 1.1 Background on Chronic Rhinosinusitis with Nasal Polyps 18
   - 1.2 Background on Omalizumab 19
   - 1.3 Study Rationale and Benefit–Risk Assessment 19
   - 1.3.1 Benefit–Risk Assessment 19

2. OBJECTIVES AND ENDPOINTS 21

3. STUDY DESIGN 24
   - 3.1 Description of the Study 24
   - 3.2 End of Study and Length of Study 26
   - 3.3 Rationale for Study Design 26
   - 3.3.1 Rationale for Omalizumab Dose and Schedule 26
   - 3.3.2 Rationale for Open-Label Study Design 27

4. MATERIALS AND METHODS 27
   - 4.1 Patients 27
   - 4.1.1 Inclusion Criteria 27
   - 4.1.2 Exclusion Criteria 28
   - 4.1.3 Omalizumab Dose Determination 28
   - 4.2 Method of Treatment Assignment and Blinding 28
   - 4.3 Study Treatment and Other Treatments Relevant to the Study Design 28
   - 4.3.1 Study Treatment Formulation, Packaging, and Handling 29
   - 4.3.1.1 Omalizumab 29
   - 4.3.1.2 Mometasone Furoate Monohydrate Nasal Spray 29
   - 4.3.2 Study Treatment Dosage, Administration, and Compliance 29
   - 4.3.3 Mometasone Furoate Monohydrate Nasal Spray 30
   - 4.3.4 Investigational Medicinal Product Accountability 30

4.3.5 Continued Access to Omalizumab 31
4.4 Concomitant Therapy 31
4.4.1 Prohibited Therapy 31
4.5 Study Assessments 32
4.5.1 Informed Consent Forms and Screening Log 32
4.5.2 Physical Examinations 32
4.5.3 Vital Signs 33
4.5.4 CRSwNP Specific Assessments 33
4.5.5 Physician Review of eDiary Data and Compliance 33
4.5.6 Laboratory, Biomarker, and Other Biological Samples 33
4.5.7 Patient-Reported Outcomes 34
4.5.7.1 Nasal Symptoms, including Nasal Congestion Score 35
4.5.7.2 Sino-Nasal Outcome Test-22 35
4.5.7.3 Patient Global Impression of Change 35
4.5.7.4 University of Pennsylvania Smell Identification Test 35
4.5.7.5 Asthma Quality of Life Questionnaire (Patients with Comorbid Asthma Only) 35
4.5.7.6 EuroQol 5-Dimension 5-Level Questionnaire 36
4.5.7.7 Medical Outcomes Study Sleep Scale 36
4.5.7.8 Healthy Days Core Module 36
4.5.8 Optional Samples for Research Biosample Repository 36
4.5.8.1 Overview of the Research Biosample Repository 36
4.5.8.2 Approval by the Institutional Review Board or Ethics Committee 37
4.5.8.3 Sample Collection 37
4.5.8.4 Confidentiality 37
4.5.8.5 Consent to Participate in the Research Biosample Repository 38
4.5.8.6 Withdrawal from the Research Biosample Repository 38
4.5.8.7 Monitoring and Oversight 39

4.6 Treatment, Patient, Study, and Site Discontinuation 39
4.6.1 Study Treatment Discontinuation 39
4.6.2 Patient Discontinuation from Study 39
4.6.3 Study Discontinuation 40
4.6.4 Site Discontinuation 40
5. ASSESSMENT OF SAFETY 40
5.1 Safety Plan 41
5.1.1 Safety and Data Monitoring 41
5.1.2 Anaphylaxis Adjudication Committee 41
5.1.3 Risks Associated with Omalizumab 41
5.1.3.1 Anaphylaxis 41
5.1.3.2 Serum Sickness 42
5.1.3.3 Churg-Strauss Syndrome and Hypereosinophilic Syndrome 43
5.1.3.4 Thrombocytopenia 43
5.1.3.5 Malignancies 43
5.1.3.6 Arterial Thrombotic Events 44
5.1.3.7 Antibody Formation to Omalizumab 44
5.1.4 Management of Patients Who Experience Specific Adverse Events 44
5.1.4.1 Dose Modifications and Treatment Interruption 44
5.1.4.2 Management of Drug Induced Liver Injuries 44
5.2 Safety Parameters and Definitions 44
5.2.1 Adverse Events 45
5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor) 45
5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor) 46
5.3 Methods and Timing for Capturing and Assessing Safety Parameters 47
5.3.1 Adverse Event Reporting Period 47
5.3.2 Eliciting Adverse Event Information 47
5.3.3 Assessment of Severity of Adverse Events 47

5.3.4 Assessment of Causality of Adverse Events 48
5.3.5 Procedures for Recording Adverse Events 48
5.3.5.1 Injection-Site Reactions 49
5.3.5.2 Anaphylactic Reactions 49
5.3.5.3 Diagnosis versus Signs and Symptoms 49
5.3.5.4 Adverse Events That Are Secondary to Other Events 49
5.3.5.5 Persistent or Recurrent Adverse Events 50
5.3.5.6 Abnormal Laboratory Values 50
5.3.5.7 Abnormal Vital Sign Values 51
5.3.5.8 Abnormal Liver Function Tests 51
5.3.5.9 Deaths 52
5.3.5.10 Preexisting Medical Conditions 52
5.3.5.11 Lack of Efficacy or Worsening of Nasal Polyposis 52
5.3.5.12 Hospitalization or Prolonged Hospitalization 52
5.3.5.13 Adverse Events Associated with an Overdose or Error in Drug Administration 53
5.3.5.14 Patient-Reported Outcome Data 53
5.4 Immediate Reporting Requirements from Investigator to Sponsor 53
5.4.1 Emergency Medical Contacts 54
5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest 55
5.4.2.1 Events That Occur prior to Study Drug Initiation 55
5.4.2.2 Events That Occur after Study Drug Initiation 55
5.4.3 Reporting Requirements for Pregnancies 55
5.4.3.1 Pregnancies in Female Patients 55
5.4.3.2 Abortions 56
5.4.3.3 Congenital Anomalies/Birth Defects 56
5.5 Follow-Up of Patients after Adverse Events 56
5.5.1 Investigator Follow-Up 56
5.5.2 Sponsor Follow-Up 56
5.6 Adverse Events That Occur after the Adverse Event Reporting Period 56

5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees 57

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN 57

6.1 Determination of Sample Size 57

6.2 Analysis Cohorts 58

6.3 Summaries of Treatment Group and Cohort Comparability 58

6.4 Summaries of Conduct of Study 59

6.5 Efficacy Analyses 59

6.5.1 Efficacy Analysis Populations 59

6.5.2 Primary Efficacy Endpoints 59

6.5.2.1 Nasal Polyp Score 60

6.5.2.2 Nasal Congestion Score 60

6.5.3 Secondary Efficacy Endpoints 61

6.5.3.1 Nasal Polyp Score and Nasal Congestion Score 61

6.5.3.2 Nasal Symptoms 61

6.5.3.3 SNOT-22, UPSIT, EQ-5D-5L, and AQLQ 62

6.5.4 Exploratory Efficacy/Psychometric Endpoints 62

6.6 Safety Analyses 62

6.6.1 Primary Safety Analysis: Adverse Events 62

6.6.2 Secondary Safety Analysis: Clinical Laboratory Evaluations 62

6.7 Pharmacokinetic/Pharmacodynamic Analyses 63

6.8 Interim Analysis 63

6.9 Missing Data 63

6.10 Unused and Spurious Data 63

7. DATA COLLECTION AND MANAGEMENT 64

7.1 Data Quality Assurance 64

7.2 Electronic Case Report Forms 64

7.3 Electronic Patient-Reported Outcome 65

7.4 Source Data Documentation 65

7.5 Use of Computerized Systems 66

7.6 Retention of Records 66

8. ETHICAL CONSIDERATIONS 66
8.1 Compliance with Laws and Regulations 66
8.2 Informed Consent 67
8.3 Institutional Review Board or Ethics Committee 68
8.4 Confidentiality 68
8.5 Financial Disclosure 69
9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION 69
9.1 Study Documentation 69
9.2 Protocol Deviations 69
9.3 Site Inspections 69
9.4 Administrative Structure 70
9.5 Publication of Data and Protection of Trade Secrets 70
9.6 Protocol Amendments 71
10. REFERENCES 72

LIST OF TABLES

Table 1 Objectives and Corresponding Endpoints 21
Table 2 Adverse Event Severity Grading Scale 47
Table 3 Causal Attribution Guidance 48

LIST OF FIGURES

Figure 1 Study Schema 26

LIST OF APPENDICES

Appendix 1 Schedule of Activities 77
Appendix 2 Omalizumab Dosing Table for Nasal Polyps 80
Appendix 3 Nasal Polyps Scoring System 81
Appendix 4 Nasal Symptoms Assessed Daily via Electronic Diary 82
Appendix 5 Nasal Symptoms Assessed via In-Clinic or Telephone Interview 83
Appendix 6 Sino-Nasal Outcome Test-22 (SNOT-22) Questionnaire 84
Appendix 7 Patient Global Impression of Change 85

Appendix 8 Asthma Quality of Life Questionnaire 86
Appendix 9 EuroQol 5-Dimension 5-Level Questionnaire 93
Appendix 10 Medical Outcomes Study Sleep Scale 95
Appendix 11 Healthy Days Core Module 97
Appendix 12 Sampson's Criteria for Diagnosing Potential Cases of Anaphylaxis 98

PROTOCOL ACCEPTANCE FORM

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TEST PRODUCT:	Omalizumab (IGE025)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

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.

Primary Safety Objective	Corresponding Endpoints
• To evaluate adverse events associated with usage of omalizumab in patients with CRSwNP	• Incidence of serious and non-serious adverse events • Incidence of adverse events leading to omalizumab discontinuation
Secondary Safety Objective	**Corresponding Endpoint**
• To evaluate any potential laboratory abnormalities associated with usage of omalizumab in patients with CRSwNP	• Clinically significant change in laboratory values
Primary Efficacy Objective	**Corresponding Endpoints [a]**
• To evaluate efficacy of continued treatment with omalizumab after an initial 24-week treatment period	• Change from baseline at Weeks 4 [b], 8 [b], 16 [b], 24 [b], 36, and 52 in NPS • Change from baseline at Weeks 4 [b], 8 [b], 12 [b], 16 [b], 20 [b], 24 [b], 28, 32, 36, 40, 44, 48, and 52 in NCS
• To evaluate the durability of response following treatment discontinuation	• Change from baseline at Weeks 52, 64, and 76 in NPS • Change from baseline at Weeks 52, 56, 60, 64, 68, 72, and 76 in NCS

Secondary Efficacy Objectives	Corresponding Endpoints [a]
• To evaluate the impact of treatment duration with omalizumab on durability of response	• Change from baseline at Week 76 in the following assessments: – NPS – NCS – TNSS – Loss of smell – Posterior rhinorrhea – Anterior rhinorrhea – SNOT-22 – EQ-5D-5L – AQLQ (patients with comorbid asthma only) – UPSIT
• To evaluate efficacy of continued treatment with omalizumab after an initial 24-week treatment period	• Change from baseline at Weeks 4 [b], 8 [b], 12 [b], 16 [b], 20 [b], 24 [b], 28, 32, 36, 40, 44, 48, and 52 in the following assessments: – TNSS – Posterior rhinorrhea – Anterior rhinorrhea – Loss of smell • Change from baseline at Weeks 4 [b], 8 [b], 16 [b], 24 [b], 36, and 52 in the following assessments: – SNOT-22 – AQLQ (patients with comorbid asthma only) • Change from baseline at Weeks 16 [b], 24 [b], 36, and 52 in EQ-5D-5L • Change from baseline at Weeks 8 [b], 16 [b], 24 [b], 36, and 52 in UPSIT

Secondary Efficacy Objectives (cont.)	Corresponding Endpoints [a] (cont.)
• To evaluate the durability of response following treatment discontinuation	• Change from baseline at Weeks 52, 56, 60, 64, 68, 72, and 76 in the following assessments: – TNSS – Posterior rhinorrhea – Anterior rhinorrhea – Loss of smell • Change from baseline at Weeks 64 and 76 in SNOT-22 • Change from baseline at Weeks 52, 64, and 76 in the following assessments: – EQ-5D-5L – AQLQ (in patients with comorbid asthma only) – UPSIT
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate efficacy of continued treatment with omalizumab after an initial 24-week treatment period	• Reduction in the need for surgery by Weeks 36 and 52, as defined by an NPS of ≤ 4 (unilateral score of ≤ 2 on each side) and improvement in SNOT-22 score of ≥ 8.9 • Requirement of rescue treatment (systemic CS for ≥ 3 consecutive days) or having had surgery for nasal polyps through Week 52 • Requirement of rescue treatment (systemic CS for ≥ 3 consecutive days) through Week 52 • Having had surgery for nasal polyps through Week 52
• To evaluate the effect of omalizumab on sleep quality after an initial 24-week treatment period of placebo	• Change from Week 24 at Weeks 36, 52, 64, and 76 in MOS Sleep Scale
• To evaluate the effect of omalizumab on overall physical and mental health after an initial 24-week treatment period of placebo	• Change from Week 24 at Weeks 36, 52, 64, and 76 in Healthy Days Core Module
Exploratory Psychometric Objective	**Corresponding Endpoint**
• To collect data to support psychometric analyses to assess sensitivity of EQ-5D-5L	• PGIC at Weeks 36, 52, 64, and 76

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.

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

[b] 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 patent 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AERD	aspirin-exacerbated respiratory disease
AQLQ	Asthma Quality of Life Questionnaire
AQLQ(S)	standardized Asthma Quality of Life Questionnaire
ATEs	arterial thrombotic events
BID	twice a day
CIU	chronic idiopathic urticaria
CRO	contract research organization
CRS	chronic rhinosinusitis
CRSwNP	chronic rhinosinusitis with nasal polyps
CS	corticosteroid
CSU	chronic spontaneous urticaria
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
eDiary	electronic diary
EQ-5D-5L	EuroQol 5-Dimension 5-level Questionnaire
EXCELS	Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma
FAS-OLE	full analysis set of the OLE study
FDA	Food and Drug Administration
FESS	functional endoscopic sinus surgery
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IWRS	interactive web-based response system
LPLV	last patient, last visit
MMRM	mixed-effect model repeated measurement
MOS	Medical Outcomes Study
NCS	nasal blockage/congestion score

NPS	nasal polyp score
OLE	open-label extension
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
PRO	patient-reported outcome
QD	once daily
QoL	quality of life
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SNOT-22	Sino-Nasal Outcome Test-22
SWFI	Sterile Water for Injection
TNSS	total nasal symptom score
ULN	upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test

1. BACKGROUND

1.1 BACKGROUND ON CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly adult disease with a prevalence estimated to be 2.1%–2.7% (Johansson et al. 2003; Klossek et al. 2005; We et al. 2015). It is associated with reduced quality of life (QoL) and significant morbidity, including asthma, which can be severe and refractory, particularly in those patients with aspirin-exacerbated respiratory disease (AERD) (Hulse et al. 2014; Stevens and Schleimer 2016).

The diagnosis of CRSwNP is made in patients who exhibit a combination of symptoms (e.g., blockage/congestion, anterior or postnasal drip, and impaired sense of smell) in the presence of nasal polyps (Fokkens et al. 2012; Rimmer et al. 2014). Intranasal and systemic/oral corticosteroids remain the mainstay of treatment, but many patients fail to achieve complete therapeutic benefit with these medications and resort to functional endoscopic sinus surgery (FESS) and other complex sinus surgery (Fokkens et al. 2012; Rimmer et al. 2014). Although FESS and intranasal and oral corticosteroids are useful and often effective in reducing the size of nasal polyps and associated symptoms, many patients do not respond sufficiently and/or polyps return rapidly after medication withdrawal or within months or years following surgery. In one trial, almost 40% of patients who received daily intranasal corticosteroids (mometasone furoate) following FESS suffered a relapse within 6 months of the procedure (Stjärne et al. 2009). In another study, almost 50% of the patients who received oral corticosteroids in combination with topical therapy suffered a relapse within 12 months of treatment (Cassano et al. 1996). Moreover, oral corticosteroids are associated with significant side effects, and repeat surgical procedures become progressively more complex and risky. In the United States, the only approved pharmacotherapy for nasal polyps is intranasal corticosteroids (mometasone furoate and/or beclomethasone). Because of limitations in treatment, combined with QoL that is considerably reduced in CRSwNP patients, nasal polyposis remains an important unmet medical need (Hulse et al. 2015).

Patients with CRSwNP and most patients with asthma share a common IgE-mediated type 2 inflammatory response, characterized by elevated levels of interleukin (IL)-4, IL-5, IL-13, eosinophils, Th2 cells, and type 2 innate lymphoid cells (Wenzel et al. 1999; Kato 2015). In addition, locally produced IgE—often against *Staphylococcus aureus* enterotoxins—is associated with local inflammation in CRSwNP and, in particular, with comorbid asthma (Bachert et al. 2010). Because of the common type 2 inflammatory disease between asthma and CRSwNP, approximately 20%–30% of patients with asthma have CRSwNP, particularly those patients with AERD. In addition, a substantial proportion of patients with CRSwNP have symptoms of asthma, with higher percentages associated with patients who have greater nasal polyp disease severity (Settipane 1987; Larsen 1996; Hedman et al. 1999; Johansson et al. 2003; Ragab et al. 2004; Pearlman et al. 2009; Promsopa et al. 2016). Importantly, there appears to be a premorbid relationship between

asthma and CRSwNP, with the diagnosis of asthma often occurring prior to that of nasal polyposis (Larsen 1996; Tan et al. 2013; Lam et al. 2014).

1.2 BACKGROUND ON OMALIZUMAB

Omalizumab (Xolair®) is a recombinant DNA-derived humanized IgG1 monoclonal antibody with a molecular mass of approximately 149 kDa that selectively binds to human IgE.

Omalizumab is designed to treat IgE-mediated disease by reducing the concentration of free IgE in blood and in tissue. Omalizumab selectively binds to human IgE at the same site as does the high affinity IgE receptor (FcεRI) (Schulman 2001), thereby reducing surface-bound IgE through this receptor on basophils and mast cells, reducing cross-linking of IgE to the receptor when antigen is bound and the subsequent basophil and mast cell triggered type 2 inflammation.

Omalizumab was approved by the U.S. Food and Drug Administration (FDA) for allergic asthma in 2003 and for chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria (CSU), in 2014.

Refer to the Omalizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This study will assess the long-term safety and tolerability of omalizumab every 2 or 4 weeks with regard to adverse events and laboratory abnormalities and will also obtain long-term data on the efficacy of omalizumab in patients with CRSwNP after participation in the Phase III studies (GA39688 or GA39855). Patients will enroll in this study following the completion of the Phase III, double-blind, placebo-controlled Study GA39688 or GA39855.

Eligible patients receiving omalizumab or placebo in the controlled Phase III study will receive active omalizumab in this study for approximately 28 weeks followed by an approximately 24-week post-treatment follow-up period. Eligibility criteria and the timepoints for enrollment in this study are described in Section 4.1.

1.3.1 Benefit–Risk Assessment

CRSwNP occurs in a subset of patients with chronic rhinosinusitis (CRS). The polyps that develop in patients with CRSwNP are characterized histologically by the presence of large numbers of eosinophils and type 2 innate lymphoid cells as well as by mucosal edema and albumin containing pseudocysts with minimal extracellular matrix fibrosis (Huvenne et al. 2009; Mjösberg et al. 2011). In contrast, nasal polyps associated with other diseases (e.g., cystic fibrosis) are associated with large numbers of neutrophils in the polyp tissue. The polyps in patients with CRSwNP exhibit a type 2 cytokine profile, with predominant expression of IL-13, IL-5, and some IL-4 (Wang et al. 2015). Activated

B cells produce IgE, often against *Staphylococcus aureus*, in association with increased mucus and chemokine production. The marked local production of IgE antibodies in patients with CRSwNP appears to be functional and involved in the regulation of chronic inflammation (Zhang et al. 2011). Asthma and CRSwNP may share similar type 2 cytokine profiles, such that a substantial proportion of patients with CRSwNP exhibit comorbid asthma. In turn, a substantial proportion of patients with asthma have CRSwNP, particularly among those with more severe asthma (Settipane 1987; Larsen 1996; Ragab et al. 2004; Pearlman et al. 2009; Langdon and Mullol 2016).

Omalizumab interrupts the allergic cascade triggered by cross-linking IgE on the surface of mast cells and basophils by 1) forming complexes with IgE and preventing the arming of effector cells; 2) aiding off-loading of mast cells and basophils by trapping IgE as it dissociates from the FcεRI receptor; 3) down-modulating FcεRI (on mast cells, basophils, and dendritic cells) as a direct consequence of the reduction in free IgE levels; 4) reducing antigen presentation to T lymphocytes by dendritic cells; 5) reducing IgE stimulated synthesis and secretion of proinflammatory cytokines by human airway smooth muscle cells; and 6) improving interferon-α production by plasmacytoid dendritic cells (Presta et al.1993; Jardieu 1995; Heusser and Jardieu 1997; Holgate et al. 1998; Fick 1999; Jardieu and Fick 1999; Patalano 1999; Boushey 2001; Prussin et al. 2003; Roth and Tamm 2010; Teach et al. 2015). These events then result in the reduction of type 2 inflammation, including reduced production of IL-4, IL-5, and IL-13 by innate and adaptive cells. Therefore, given the multiple potential mechanisms of omalizumab in limiting the inflammation in nasal polyps, a strategy to antagonize IgE with omalizumab is likely to benefit patients with CRSwNP.

The benefit of antagonizing IgE in patients with CRSwNP has also been suggested by a randomized, double-blind, placebo-controlled study in patients with nasal polyps and comorbid asthma published by Gevaert et al. 2013. Twenty-four patients (nasal polyp size $\geq$5) were included and randomized 2:1 to receive omalizumab or placebo for 16 weeks. Twelve of the 24 patients had the diagnosis of aspirin hypersensitivity. Results showed a significant reduction from baseline in total nasal endoscopic polyp score in patients in the omalizumab group at Week 16 (-2.67, $p=0.001$) but not in patients in the placebo group (-0.12, $p=0.99$). In addition, omalizumab treatment improved computed tomography image scores; reduced symptom scores for nasal congestion, anterior rhinorrhea, loss of sense of smell, wheeze, and dyspnea; and improved QoL scores, all irrespective of the presence of allergy (Gevaert et al. 2013).

A number of other case-controlled and randomized, double-blind, placebo-controlled studies have been performed over the past decade examining the efficacy of omalizumab for the treatment of nasal polyps (Penn and Mikula 2007; Pinto et al. 2010; Vennera et al. 2011; Tajiri et al. 2013; Sintobin et al. 2015). The collective and cumulative clinical evidence strongly suggests a potential benefit of omalizumab in patients with CRSwNP.

Omalizumab is being investigated in placebo-controlled randomized clinical trials (Studies GA39688 and GA39855), which will provide the source population for this current extension study. These studies are enrolling patients with difficult-to-treat CRSwNP, large bilateral nasal polyps, and substantial burden to their heath-related quality of life (HRQoL). As such, it is anticipated that patients may potentially require longer-term treatment of their CRSwNP with a biologic medication and that the usage of such biologic medications longer than 24 weeks may be warranted in some situations. Moreover, omalizumab may be utilized longer term for the other two indications for which it is approved: allergic asthma and CIU/CSU. There is indeed significant evidence regarding omalizumab's longer-term safety profile, including the Epidemiologic Study of Xolair (Omalizumab): Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate-to-Severe Asthma (EXCELS), a prospective observational cohort study of adults and adolescents with allergic asthma with a median follow-up of 5 years including 5007 patients in an omalizuamb cohort and 2829 patients in a comparator non-omalizumab cohort (Long et al. 2014).

Thus, the studies that provide evidence for potential effectiveness of anti-IgE therapy in CRSwNP, the enrollment of difficult-to-treat patients with significant disease burden, the established safety profile of omalizumab, and omalizumab's frequent longer-term usage in other indications provide evidence for the benefit–risk assessment of conducting the current extension study.

2. 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 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 (see Table 1).

Table 1 Objectives and Corresponding Endpoints

Primary Safety Objective	Corresponding Endpoints
• To evaluate adverse events associated with usage of omalizumab in patients with CRSwNP	• Incidence of serious and non-serious adverse events • Incidence of adverse events leading to omalizumab discontinuation
Secondary Safety Objective	**Corresponding Endpoint**
• To evaluate any potential laboratory abnormalities associated with usage of omalizumab in patients with CRSwNP	• Clinically significant change in laboratory values

Primary Efficacy Objective	Corresponding Endpoints [a]
• To evaluate efficacy of continued treatment with omalizumab after an initial 24-week treatment period	• Change from baseline at Weeks 4 [b], 8 [b], 16 [b], 24 [b], 36, and 52 in NPS • Change from baseline at Weeks 4 [b], 8 [b], 12 [b], 16 [b], 20 [b], 24 [b], 28, 32, 36, 40, 44, 48, and 52 in NCS
• To evaluate the durability of response following treatment discontinuation	• Change from baseline at Weeks 52, 64, and 76 in NPS • Change from baseline at Weeks 52, 56, 60, 64, 68, 72, and 76 in NCS
Secondary Efficacy Objectives	**Corresponding Endpoints [a]**
• To evaluate the impact of treatment duration with omalizumab on durability of response	• Change from baseline at Week 76 in the following assessments: – NPS – NCS – TNSS – Loss of smell – Posterior rhinorrhea – Anterior rhinorrhea – SNOT-22 – EQ-5D-5L – AQLQ (patients with comorbid asthma only) – UPSIT
• To evaluate efficacy of continued treatment with omalizumab after an initial 24-week treatment period	• Change from baseline at Weeks 4 [b], 8 [b], 12 [b], 16 [b], 20 [b], 24 [b], 28, 32, 36, 40, 44, 48, and 52 in the following assessments: – TNSS – Posterior rhinorrhea – Anterior rhinorrhea – Loss of smell • Change from baseline at Weeks 4 [b], 8 [b], 16 [b], 24 [b], 36, and 52 in the following assessments: – SNOT-22 – AQLQ (patients with comorbid asthma only) • Change from baseline at Weeks 16 [b], 24 [b], 36, and 52 in EQ-5D-5L • Change from baseline at Weeks 8 [b], 16 [b], 24 [b], 36, and 52 in UPSIT

Secondary Efficacy Objectives (cont.)	Corresponding Endpoints [a] (cont.)
• To evaluate the durability of response following treatment discontinuation	• Change from baseline at Weeks 52, 56, 60, 64, 68, 72, and 76 in the following assessments: – TNSS – Posterior rhinorrhea – Anterior rhinorrhea – Loss of smell • Change from baseline at Weeks 64 and 76 in SNOT-22 • Change from baseline at Weeks 52, 64, and 76 in the following assessments: – EQ-5D-5L – AQLQ (in patients with comorbid asthma only) – UPSIT
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate efficacy of continued treatment with omalizumab after an initial 24-week treatment period	• Reduction in the need for surgery by Weeks 36 and 52, as defined by an NPS of ≤ 4 (unilateral score of ≤ 2 on each side) and improvement in SNOT-22 score of ≥ 8.9 • Requirement of rescue treatment (systemic CS for ≥ 3 consecutive days) or having had surgery for nasal polyps through Week 52 • Requirement of rescue treatment (systemic CS for ≥ 3 consecutive days) through Week 52 • Having had surgery for nasal polyps through Week 52
• To evaluate the effect of omalizumab on sleep quality after an initial 24-week treatment period of placebo	• Change from Week 24 at Weeks 36, 52, 64, and 76 in MOS Sleep Scale
• To evaluate the effect of omalizumab on overall physical and mental health after an initial 24-week treatment period of placebo	• Change from Week 24 at Weeks 36, 52, 64, and 76 in Healthy Days Core Module
Exploratory Psychometric Objective	**Corresponding Endpoint**
• To collect data to support psychometric analyses to assess sensitivity of EQ-5D-5L	• PGIC at Weeks 36, 52, 64, 76

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.

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

[b] These data are from Studies GA39688/GA39855.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE 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.

Written informed consent for participation in the study must be obtained before performing any study-specific tests or evaluations. Patients will then start receiving open-label omalizumab as per the dosing schedule based on their body weight and IgE levels collected during the screening period of Study GA39688/GA39855 (see Figure 1). Patients will also undergo assessments as shown in the schedules of activities in Appendix 1.

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 (see Appendix 2).

Patients should remain on stable doses of intranasal corticosteroid (CS) therapy (mometasone nasal spray 200 μg twice a day [BID] as per Section 4.3.3) 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 (see Appendix 1).

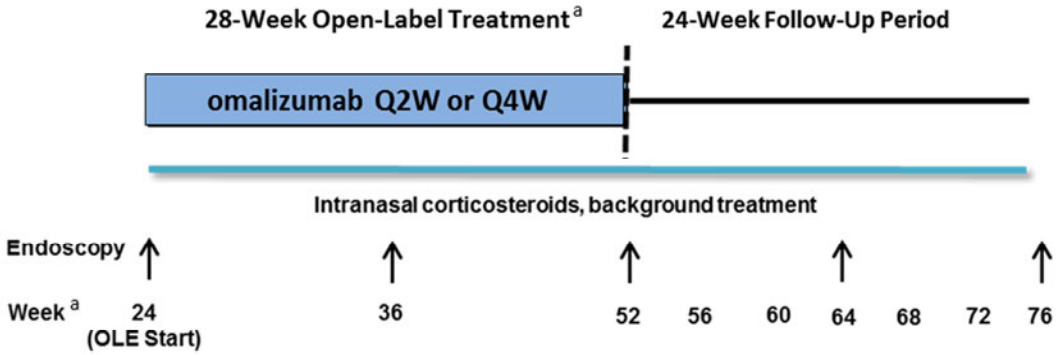
After the treatment period ends (after Week 52 Visit), patients will be followed for an additional 24 weeks as part of the follow-up period (Appendix 1). There is no dose administered at Week 52. During the follow-up period, patients will be asked to continue completion of their daily electronic diary (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.

NPS will be assessed by video nasal endoscopy, scored using a standard scoring system (Appendix 3; 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).

A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



OLE = open-label extension; Q2W = every 2 weeks; Q4W = every 4 weeks.

[a] The timing of the visit schedule is defined in time relative to the baseline of Study GA39688/GA39855. Thus, the open-label treatment period of this study is 28 weeks and runs from the "Week 24 Visit" (approximately 24 weeks after initiation of study drug in Study GA39688/GA39855) to the "Week 52 Visit" (approximately 52 weeks after initiation of study drug in Study GA39688/GA39855).

3.2 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 patent is enrolled (28-week treatment period of OLE followed by 24-week follow-up period).

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Omalizumab Dose and Schedule

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 Study GA39688/GA39855 (see Section 4.1.3 for further details). Omalizumab will be dosed according to the same dosing table used in Study GA39688/GA39855. That is, dosing will be based on a dosing table that provides at least 0.016 mg/kg for every IU/mL of IgE, within a 4-week interval (see Appendix 2). The dosing algorithm used as the basis of the dosing table is consistent with the approach used in published studies for the treatment of CRSwNP and with the approach used for the treatment of allergic asthma. The range of IgE values (30 IU/mL to 1,500 IU/mL) used in the dosing table comes from the asthma E.U. SmPC dosing table. This asthma E.U. SmPC table has been modified to remove lower patient weights because this trial will include only adult patients, whereas the approved asthma E.U. SmPC table is also intended to treat pediatric patients. As with the approved E.U. SmPC table, omalizumab will be administered every 4 weeks for doses up to and including 600 mg and every 2 weeks for those patients requiring higher doses (see Appendix 2).

3.3.2 Rationale for Open-Label Study Design

For the purposes of efficacy analyses, this study utilizes endpoints such as nasal blockage/congestion score (NCS) and NPS with continuous outcomes scales rather than binary event rates. These outcomes are evaluated over time, as detailed in Section 6.6, allowing an examination of the extent to which patients improve or worsen relative to a previous point in time. In addition, providing omalizumab to all patients in this study provides larger sample sizes for analyses such as durability of response, relative to designs such as a randomization–withdrawal approach. Moreover, this open-label design will allow an examination of the impact of longer treatment duration on durability of response, as discussed in Section 6.5.3.1.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will enroll patients from the double-blind, placebo-controlled, Phase III Study GA39688/GA39855 who have completed study treatment. These patients may enroll in this open-label study at the Week 24 visit of Study GA39688 or GA39855, or within 7 calendar days after the Week 24 visit (see Section 3.1 for further explanation). Patients must complete the Week 24 visit (and the assessments at this visit) of either Study GA39688 or Study GA39855 in order to be eligible to enroll into this study.

4.1.1 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.

4.1.2 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

4.1.3 Omalizumab Dose Determination

Serum total IgE levels and body weight from the screening data from Study GA39688/GA39855 will be used to determine patient's eligibility for the study and determination of omalizumab dose. The serum total IgE levels and body weight should be based on the values from Day -35 of Study GA39688/GA39855 unless values from alternate timepoints during the screening period of those studies were utilized for the determination of study drug dosing in Study GA39688/GA39855 (e.g., because of missing values at Day -35).

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

As this is an open-label study, all patients will receive omalizumab. To maintain the blind to the treatment assignment of the previous Study GA39688/GA39855, there will be no adjustment in dosing from those doses assigned in Study GA39688/GA39855, which are based on values of total IgE and body weight from the screening period of Study GA39688/GA39855.

To minimize bias in this study, patients and the evaluating physicians will be blinded to treatment assignment of the previous Study GA39688/GA39855 until all patients have either completed the study through the follow-up period (Week 76) or discontinued early from the study, the database is locked, and the study analyses are final.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Omalizumab

Omalizumab will be supplied by the Sponsor. Omalizumab is a sterile, white, preservative-free, lyophilized powder, contained in a single-use vial that will be reconstituted with Sterile Water for Injection (SWFI), USP, and administered as an SC injection. Each omalizumab vial contains 202.5 mg of omalizumab, 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20. Each vial is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP. For additional details, see the pharmacy manual and the Omalizumab Investigator's Brochure.

4.3.1.2 Mometasone Furoate Monohydrate Nasal Spray

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

Each spray delivers 50 μg of mometasone furoate monohydrate per actuation. Sites are responsible for ensuring patients have access to the required mometasone furoate monohydrate nasal spray. The nasal spray should be stored appropriately as per the local prescribing information.

Any adverse events associated with an overdose or incorrect administration of mometasone furoate monohydrate nasal spray should be recorded on the Adverse Event electronic Case Report Form (eCRF).

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimen is summarized in Section 3.1.

Any overdose or incorrect administration of omalizumab should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.4.

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.

Patients should be observed after administration of omalizumab for signs and symptoms of anaphylaxis. More details are provided in Section 5.1.3.1. In addition, the study staff should be prepared to manage anaphylaxis. Patients should also be informed of the

signs and symptoms of anaphylaxis and be instructed to seek immediate care should symptoms occur.

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 via central laboratory) and body weight (kg) as specified in Appendix 2. Both IgE level and body weight used for dosing will be based on values obtained during the screening period of Study GA39688/GA39855 as per Section 4.1.3. Assignment of omalizumab dose will be determined by using the dosing table in Appendix 2. 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.

Study drug kits must be stored at 2°C–8°C (36°F–46°F) in refrigerated conditions in a limited access area and/or a locked refrigerator. Study drug should not be frozen or shaken. Study drug should be stored immediately upon receipt but no later than 24 hours after receipt. Omalizumab is for single-use only and contains no preservatives. The solution may be used for SC administration within 8 hours following reconstitution if stored in the vial at 2°C–8°C (36°F–46°F) or within 4 hours of reconstitution if stored at room temperature. For further details on drug handling, see the pharmacy manual.

4.3.3 Mometasone Furoate Monohydrate Nasal Spray

All patients will be required to continue mometasone furoate nasal spray (e.g., Nasonex®), as taken during Study GA39688/GA39855, throughout the duration of the study period, including the follow-up period from Week 52 through Week 76. As in Study GA39688/GA39855, patients will take two sprays/nostril, both nostrils, 50 μg/spray BID for a total daily dose of 400 μg. Patients deemed by the investigator to be intolerant to a BID regimen of mometasone may be treated with a stable dosage of mometasone 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 this OLE study.

Patient adherence to prescribed mometasone regimen will be assessed by the investigator at clinic visits and recorded in the appropriate eCRF.

For more information on formulation, dosing, and product safety, see the local prescribing information for mometasone furoate nasal spray.

4.3.4 Investigational Medicinal Product Accountability

The IMP (omalizumab) required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of the IMP supplied by the sponsor using the interactive web-based response system (IWRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Continued Access to Omalizumab

Currently, the Sponsor does not have any plans to provide the Roche IMP omalizumab or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing omalizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from Day -35 (1st screening visit). All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy other than the study drug
- Sino-nasal surgical procedures, including polypectomies

  Patients requiring sino-nasal surgery (e.g., nasal polypectomy) during the study should have their reasons for surgery documented and reviewed by the Medical Monitor. Should surgery occur during the treatment phase, study medication should be discontinued, although study assessments should continue. Should the patient elect to withdraw from study medication, the safety follow-up visits should be scheduled. Details of the surgical procedure should be recorded on the eCRF.
- Any intranasal corticosteroids other than that required by the protocol
- Any parenteral steroid injections such as triamcinolone
- Use of verapamil
- Use of cyclosporine, methotrexate, azathioprine, or mycophenolate and chronic use of systemic corticosteroids

Acute courses of oral or systemic corticosteroids must be justified and reasons documented.

- Changes in allergen immunotherapy or initiation of new allergen immunotherapy
- Changes in aspirin desensitization therapy or initiation of new aspirin desensitization therapy
- Use of systemic antibiotics for $>$ 14 days
- Intranasal medication that may interfere with the symptoms of diseases (antihistamines, nasal atropine, ipratropium bromide, nasal cromolyn, intranasal antibiotics like mupirocin irrigation), except nasal saline
- Nasal decongestants except when administered by study personnel on the day of endoscopy immediately prior to such endoscopy

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. To ensure PRO instrument validity and that data standards meet health authority requirements, the questionnaires that will be completed at certain site visits (e.g., Sino-Nasal Outcome Test-22 [SNOT-22], EuroQol 5 Dimension, 5-Level Questionnaire [EQ-5D-5L], University of Pennsylvania Smell Identification Test [UPSIT], Asthma Quality of Life Questionnaire [AQLQ; for patients with comorbid asthma only], Medical Outcomes Study [MOS] Sleep Scale, Healthy Days Core Module) must be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments and prior to the administration of study treatment, unless otherwise specified.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed consent forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Physical Examinations

Limited, symptom-directed physical examinations should be performed at specified visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.3 Vital Signs

Vital signs will include measurements of pulse rate and systolic and diastolic blood pressure while the patient is in a seated position. Blood pressure and pulse rate should be assessed prior to all study drug administrations.

4.5.4 CRSwNP Specific Assessments

The following measures of CRSwNP will be collected during the study:

- NPS will be assessed by video nasal endoscopy (0–4 scale on each side). Nasal endoscopy (including use of decongestants before the procedure) will be performed after all other efficacy assessments have been completed for each visit. In cases where nasal endoscopy is performed at a different location than the primary Principal Investigator site, endoscopy can be performed subsequent to the main site visit (within 3 days). Standardized video files will be uploaded by the investigator or the assigned nasal endoscopist to the central reader's secured Internet site (see Appendix 3 for nasal polyp scoring system and the nasal endoscopy site manual for more details).
- Nasal symptoms including NCS (see Section 4.5.7.1 and Appendix 4)
- SNOT-22 (see Section 4.5.7.2 and Appendix 6)
- UPSIT (see Section 4.5.7.4)
- Patient Global Impression of Change (PGIC) (see Section 4.5.7.3 and Appendix 7)

4.5.5 Physician Review of eDiary Data and Compliance

Electronic data from the eDiary will be transferred to a web-based platform for review.

Study site personnel (e.g., investigator) should review eDiary adherence to completion of eDiary at least once every 4 weeks, including during the follow-up period. Patients with poor eDiary adherence should be reminded during their clinic or telephone interviews about the importance of completing these assessments.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Urine pregnancy test
  - All women of childbearing potential should have a urine pregnancy test prior to the initiation of study drug, every 4 weeks during the study treatment period, and during the follow-up period, as indicated in Appendix 1. Urine pregnancy test results must be reviewed and confirmed to be negative before administering study drug in this study. If a urine pregnancy test is positive or borderline, it must be confirmed by a serum pregnancy test (analyzed at the central laboratory) before giving study drug.

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis.

- Standard hematology, including but not limited to: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Standard chemistry panel (serum or plasma), including but not limited to: sodium, potassium, chloride, bicarbonate, glucose, BUN/urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, LDH

Samples for the following laboratory tests will be sent to the sponsor or a designee for analysis:

- Serum samples for pharmacokinetic (PK) and anti-drug antibody (ADA) analysis. PK samples may also be used for additional drug level/ADA testing. During the open-label treatment period, the PK and ADA samples need to be drawn before administration of omalizumab.
- Serum samples for determination of trough serum free-IgE and serum total-IgE. The IgE samples may also be used for specific IgE testing, including but not limited to specific IgE to *Staphylococcus aureus* enterotoxin. The samples from PK, ADA, and IgE testing will be destroyed no later than 5 years after the final Clinical Study Report has been completed, unless the patient gives specific consent for his or her residual samples to be donated for optional exploratory research. During the open-label treatment period, the samples need to be drawn before administration of omalizumab.

4.5.7 Patient-Reported Outcomes

PRO questionnaires will be translated into the local language as appropriate and will be completed in their entirety at specified timepoints during the study, as outlined in Appendix 1. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered early in the clinic visit, before the patient receives any information on his or her disease status and prior to the performance of non-PRO assessments (e.g., endoscopy, UPSIT), unless otherwise specified. Additionally, PROs should be collected prior to the administration of study treatment.

Patients will complete specific PRO assessments on a daily basis in the morning. For such daily PRO assessments, patients will use an eDiary. Patients will be instructed to complete the questions in their eDiary in the morning, within approximately 1 hour of awakening. The device will be programmed to lock data entry in the afternoon. The electronic device and/or instructions for completing the questionnaires electronically will be provided by site staff. During the treatment and follow-up periods, nasal symptoms will also be collected via interview at site visits and entered into the electronic data capture (EDC) system. The data will be transmitted to a centralized database

maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

4.5.7.1 Nasal Symptoms, including Nasal Congestion Score

Patient-reported nasal symptoms (nasal congestion, sense of smell, anterior rhinorrhea, posterior rhinorrhea) will be scored as not at all, mild, moderate, or severe (scores of 0, 1, 2, or 3, respectively). Total nasal symptom score (TNSS) consists of nasal congestion, loss of smell, and rhinorrhea. Symptoms will be reported by patients daily (in the morning) on an eDiary, through treatment and follow-up periods. The nasal symptom questions, which include NCS, are provided in Appendix 4.

Additionally, during specific visits, as indicated in Appendix 1, these patient-reported nasal symptoms will also be collected by site staff in clinic or by telephone, via interview with a 1-week recall period. The interview nasal symptom assessment questions are provided in Appendix 5.

4.5.7.2 Sino-Nasal Outcome Test-22

SNOT-22 (Hopkins et al. 2009) utilizes a 2-week recall period to measure common symptoms of CRS with and without nasal polyps (nasal blockage, facial pain, sense of smell, drainage, need to blow nose, sneezing, runny nose, and sleep and emotional issues; see Appendix 6).

The 22 items are summed to provide a total score, with a lower score indicating fewer problems and better HRQoL. The SNOT-22 will be completed electronically at specified timepoints, as outlined in the schedule of activities (see Appendix 1).

4.5.7.3 Patient Global Impression of Change

The PGIC is a single-item assessment of the patient's impression of his or her change in nasal polyp symptoms since the previous study visit. Change in nasal polyps symptoms is rated on a seven-point scale ranging from very much worse to very much improved. The PGIC will be administered at specific visits specified in the schedule of activities (see Appendix 1). A copy of the PGIC is provided in Appendix 7.

4.5.7.4 University of Pennsylvania Smell Identification Test

The UPSIT (Doty et al. 1984) is a 40-item objective assessment of sense of olfactory function. It is a self-administered "scratch-and-sniff" test. The UPSIT is provided in booklets that have 40 microencapsulated odorants, each with a multiple-choice option for the response. The number of correct responses is summed to provide a total score. The UPSIT will be completed at clinic visits at specified timepoints, as outlined in the schedule of activities (see Appendix 1).

4.5.7.5 Asthma Quality of Life Questionnaire (Patients with Comorbid Asthma Only)

The standardized AQLQ (AQLQ[S]) will be completed by patients with comorbid asthma in order to assess the patients' asthma-specific HRQoL (Juniper et al. 1999). The

32-item questionnaire contains four domains: activity limitations, symptoms, emotional function, and environmental stimuli. The AQLQ(S) has a recall specification of 2 weeks. Items are scored on a seven-point scale ranging from 1 (severe impairment) to 7 (no impairment). A copy of the AQLQ(S) is provided in Appendix 8.

4.5.7.6 EuroQol 5-Dimension 5-Level Questionnaire

The EQ-5D-5L is a self-reported health status questionnaire that consists of six questions that are used to calculate a health utility score for use in health economic analysis (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; Appendix 9). Patients will complete the EQ-5D-5L at specific visits as specified in the schedule of activities (see Appendix 1).

There are two components to the EuroQol EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as a visual analogue scale that measures health state. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D-5L will be utilized in this study for economic modeling.

4.5.7.7 Medical Outcomes Study 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 (Hays and Stewart 1992; Spritzer and Hays 2003). 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 (see Appendix 10).

4.5.7.8 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 (see Appendix 11). Patients will complete the Healthy Days Core Module at specific visits as specified in the schedule of activities (see Appendix 1).

4.5.8 Optional Samples for Research Biosample Repository

4.5.8.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be stored from patients who give specific consent to donate samples for research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.8.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.8) will not be applicable at that site.

4.5.8.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research related to omalizumab or CRSwNP and related diseases:

- Residual blood, serum, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including residual PK and ADA serum

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.8.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.8.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.8.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent from the RBR at any time for any reason. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study WA40169 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study WA40169.

4.5.8.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced. Patients who discontinue study treatment should continue with remaining study assessments as per Appendix 1.

Patients who do not wish to continue with study assessments will return to the clinic for a dosing termination visit within 28 days after the last dose of study drug and will then subsequently return for a safety follow-up visit (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who discontinue from the study. The patient should be asked to return for a study discontinuation visit within

28 days after the last dose of study drug and then return for a safety follow-up visit. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

Omalizumab is not approved for the treatment of adult patients with CRSwNP who have had an inadequate response to standard-of-care treatments. The safety plan for patients in this study is based on the extensive clinical and postmarketing experience with omalizumab for the last 13 years. Omalizumab is marketed in over 90 countries for allergic asthma and 80 countries for CIU/CSU as of 31 December 2016. The estimated cumulative omalizumab exposure is 31,000 Patient-Years in clinical trials and 819,000 Patient-Years in the postmarketing setting as of 31 December 2016.

The clinical safety of omalizumab has been well documented in a number of clinical trials that involve adults and children with moderate to severe allergic asthma. The adverse event profile of omalizumab observed during the clinical development program of allergic asthma was similar to placebo, with the most commonly reported adverse events being headaches and injection site reactions, including injection site pain, swelling, erythema, pruritus. Anaphylactic reactions were observed but were rare and typically occurred within 2 hours of the first injection. The overall adverse event profile in CIU/CSU studies

was consistent with the known safety profile of omalizumab. Omalizumab has also been investigated in patients with seasonal allergic rhinitis, perennial allergic rhinitis, atopic dermatitis, and peanut allergy. The safety profile of omalizumab in non-asthma trials has not differed from the safety profile of omalizumab in asthma trials.

The Sponsor does not anticipate a difference in the safety profile of omalizumab in the population with nasal polyps from the existing safety profile in asthma and CIU/CSU where the safety profile of the molecule is already well defined. No specific safety concerns were identified in the published literature for the similar indication and study population with omalizumab.

5.1 SAFETY PLAN

The anticipated important safety risks for omalizumab are outlined below. Please refer to the omalizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, is provided appropriately (see Section 4.6).

5.1.1 Safety and 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 in this study.

5.1.2 Anaphylaxis Adjudication Committee

All potential anaphylaxis cases reported by investigators to the Sponsor will be subsequently submitted for adjudication to a blinded 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 12) and whether the reported anaphylaxis event is causally related to study drug. Further details will be provided in the Anaphylaxis Adjudication Charter.

5.1.3 Risks Associated with Omalizumab

5.1.3.1 Anaphylaxis

Anaphylaxis has been reported to occur after administration of omalizumab in clinical trials and in postmarketing spontaneous reports. Anaphylactic reactions were rare in clinical trials (0.1%) and estimated as 0.2% from postmarketing reporting. The reported

signs and symptoms included, but were not limited to, bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been reported as life threatening.

The majority of anaphylactic-type reactions have been reported to occur after the first dose, with numbers decreasing with subsequent doses, but such reactions were also reported beyond 1 year after starting scheduled treatment. The events were reported to occur predominantly within the first 2 hours post-dose, with few reports occurring as far as > 36 hours post-dose.

Details regarding management of these events are provided below:

- Administer omalizumab only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening; medications for the treatment of anaphylactic reactions should be available for immediate use following administration of omalizumab.
- Patients should be observed for at least 2 hours after the first 3 study drug doses, within this OLE study, and at least 30 minutes after subsequent doses. However, some patients may require longer observation periods, depending on investigator judgment taking into account the time to onset of anaphylaxis seen in clinical trials and postmarketing spontaneous reports. The American College of Allergy, Asthma, and Immunology guideline on the observation period after omalizumab administration (Kim et al. 2010) recommends 2 hours of monitoring in the clinic after the first three injections and 30 minutes or an appropriate time agreed upon by the individual patient and healthcare professional for subsequent injections. However, a delayed onset of symptoms and protracted progression of anaphylaxis should be taken into account when administering omalizumab (Limb et al. 2007).
- Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur.
- Discontinue omalizumab in patients who experience a severe hypersensitivity (anaphylactic) reaction.

5.1.3.2 Serum Sickness

Serum sickness and serum sickness–like reactions, which are delayed allergic type III reactions, have rarely been seen in patients treated with humanized monoclonal antibodies including omalizumab in the post-approval use. The onset has typically been 1–5 days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis/arthralgia, rash (urticaria or other forms), fever, and lymphadenopathy. Antihistamines and corticosteroids may be useful for preventing or treating this disorder.

- Patients should be informed and advised to report any suspected symptoms of serum sickness–like reactions.
- Physicians should stop omalizumab if a patient develops this constellation of signs and symptoms.

5.1.3.3 Churg-Strauss Syndrome and Hypereosinophilic Syndrome

Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids. In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy and alerted to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy.

Abrupt discontinuation of systemic or inhaled corticosteroids after initiation of omalizumab therapy is not recommended. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually. Patients with known or suspected Churg-Strauss syndrome should be excluded from the study.

5.1.3.4 Thrombocytopenia

In nonclinical studies, a dose-dependent and reversible circulating platelet reduction was observed. In clinical studies, few patients experienced platelet counts below the lower limit of the normal laboratory range. None of these changes was associated with bleeding episodes or a decrease in hemoglobin.

5.1.3.5 Malignancies

During initial clinical trials in adults and adolescents 12 years of age and older with allergic asthma, there was a numerical imbalance in cancers arising in the active treatment group compared with the control group. The number of observed cases was uncommon ($<$ 1/100) in both the active and the control group. In a subsequent observational study (EXCELS) comparing 5007 omalizumab-treated patients and 2829 non-omalizumab-treated patients followed for up to 5 years, the incidence rates of primary malignancies per 1000 patient years were 16.01 (295/18,426 patient years) and 19.07 (190/9963 patient years), respectively, which does not indicate an increased malignancy risk (rate ratio 0.84, 95% CI: 0.62–1.13). In a further analysis of randomized double-blind placebo-controlled clinical trials, including 4254 patients on omalizumab and 3178 patients on placebo, omalizumab treatment was not associated with an increased malignancy risk based on incidence rates per 1000 patient years of 4.14 (14/3382 patient years) for omalizumab-treated patients and 4.45 (11/2474 patient years) for placebo patients (rate ratio 0.93, 95% CI: 0.39–2.27). The overall observed incidence rate of malignancy in the omalizumab clinical trial program was comparable to that reported in the general population. There were no cases of malignancy in clinical trials in allergic asthma in the 6 to $<$ 12 years-of-age group with omalizumab; there were 2 cases of malignancy in the control group (medulloblastoma and nephroblastoma).

In the Phase III CIU/CSU program (733 patients enrolled and receiving at least 1 dose of omalizumab, including 684 patients exposed for 12 weeks and 427 exposed for

24 weeks), there was 1 case of malignancy in the placebo group (242 patients) and 1 case in the omalizumab 300-mg group (412 patients) in a patient with a preexisting history.

5.1.3.6 Arterial Thrombotic Events

In controlled clinical trials in allergic asthma and during interim analyses of EXCELS (an observational study), a numerical imbalance of arterial thrombotic events (ATEs) was observed. ATEs included stroke, transient ischemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). The results from EXCELS revealed the rate of ATEs per 1,000 patient years was 7.52 (115/15,286 patient years) for omalizumab-treated patients and 5.12 (51/9,963 patient years) for control patients. Although there was no consistent evidence of an association between omalizumab use and risk of ATEs, the 95% CIs were wide and could not definitively exclude an elevated risk.

5.1.3.7 Antibody Formation to Omalizumab

Omalizumab is a humanized monoclonal anti-IgE antibody. The formation of anti-omalizumab antibodies (also called ADAs) after omalizumab administration is a rare event. There were 3 ADA-positive cases out of 23,375 serum samples tested in the Allergic Asthma and CSU/CIU programs following omalizumab administration. These cases were not associated with any severe adverse events.

There was no case of drug-induced ADAs recorded across the entire CSU/CIU development program.

5.1.4 Management of Patients Who Experience Specific Adverse Events

5.1.4.1 Dose Modifications and Treatment Interruption

No dose modification or treatment interruption is allowed during the conduct of the study. Omalizumab should be discontinued in patients who experience a severe hypersensitivity reaction.

5.1.4.2 Management of Drug Induced Liver Injuries

Liver injury has not been described as a risk associated with omalizumab. However, 1) if the patient's AST or ALT is $>8\times$ upper limit of normal (ULN), or 2) if the patient's AST or ALT $>3\times$ ULN and total bilirubin $>2\times$ ULN or clinical jaundice occurs, study drug should be discontinued, liver test should be repeated, and an evaluation for causes for the liver test abnormality should be initiated.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events (including serious adverse events and adverse events of special interest), performing protocol-specified safety laboratory assessments, measuring protocol-specified vital

signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.2.2.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.11.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., nasal endoscopy)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Suspected anaphylaxis/anaphylactoid reactions identified based on Sampson's criteria (see Appendix 12)
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until the end of the safety follow-up period (Week 76). Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 2 will be used for assessing severity of adverse events.

Table 2 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection-Site Reactions

Local adverse events that occur during (or within 24 hours) after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction" on the Adverse Event eCRF). Associated signs and symptoms should be recorded on the dedicated Injection-Site Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection-Site Reaction eCRF.

5.3.5.2 Anaphylactic Reactions

The investigator should use Sampson's criteria (Appendix 12) to identify the potential cases of anaphylaxis and report as a diagnosis on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Any case of known or suspected anaphylaxis will require the completion of a dedicated eCRF to record the specific signs and symptoms associated with this event.

5.3.5.3 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.

- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory

abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of

the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of Nasal Polyposis

Medical occurrences or symptoms of deterioration that are anticipated as part of nasal polyposis should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of nasal polyposis on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "worsening of nasal polyposis as compared to baseline").

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse

event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol if required by site (e.g., for study drug administration or nasal endoscopy)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.13 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.14 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take

place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information (Primary)

Medical Monitor:	[redacted], M.D.
	PPD [redacted]
Telephone No. (24/7) North America:	(888) 483-7729
Telephone No. (24/7) Europe:	+44 1223 374 240

Additional contact information will be provided by the Sponsor as needed.

Questions and issues related to medical monitoring may be directed to the above numbers, which are available 24 hours per day, 7 days per week.

Roche Medical Monitor Contact Information (Secondary)

Roche Medical Responsible:	[redacted], M.D.
Telephone No.:	[redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, all adverse events including serious adverse events, non-serious events, and adverse events of special interest will be reported until completion of the follow-up period. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur post-study are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 60 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the

investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as study completion date), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper

Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Omalizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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. Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP). The SAP may be reviewed by health authorities and will be finalized prior to database lock. To allow for incorporation of health authority input, the statistical methods in the SAP may differ from and will supersede those described in this document.

Throughout this Section the term "descriptive statistics" is defined as follows, unless otherwise noted:

- For continuous variables descriptive statistics will include at a minimum: number of subjects, mean, standard deviation, median, minimum, and maximum.
- For categorical variables descriptive statistics will include at a minimum: number of patients and percentage of patients.

6.1 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.

6.2 ANALYSIS COHORTS

The study population 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

6.3 SUMMARIES OF TREATMENT GROUP AND COHORT COMPARABILITY

The two previous studies (GA39688 and GA39855) from which the current study population is drawn are planned to be identical with respect to all design considerations including:

- Geographic regions (North America, ex-North America)
- Schedule of assessments
- Inclusion/exclusion criteria
- Treatment regimen based on the omalizumab dosing table (see Appendix 2)

Therefore, baseline characteristics, study conditions, and treatment regimen characteristics are expected to be similar between the two trials as characterized by:

- Number of injections received
- Number of patients in each dosing schedule (e.g., Q2W, Q4W)
- Relative dose intensity (e.g., the amount of study drug administered divided by the amount of study drug planned)

To ensure comparability of study treatment, Cohorts A and Cohort B baseline characteristics (e.g., age, sex, race/ethnicity, NPS, NCS, sense of smell, anterior rhinorrhea, posterior rhinorrhea, and SNOT-22) will be summarized in all patients with data using descriptive statistics both by cohort and by previously-randomized treatment group within cohort (omalizumab and placebo). Prior study treatment characteristics will be compared by descriptive statistics across cohorts (e.g., omalizumab from Cohort A with omalizumab from Cohort B) to control for potential confounding of different early withdrawal rates by treatment groups. Baseline disease characteristics for each cohort (e.g., NCS, NPS, SNOT-22, etc.) will be defined as the last measurement prior to randomization in the previous study (GA39688, GA39855).

6.4 SUMMARIES OF CONDUCT OF STUDY

Descriptive statistics will be used to evaluate the conduct of the study. The number of patients enrolled will be tabulated by study site and by treatment randomized (omalizumab or placebo) in the previous study in all patients with data. Patient disposition (the number of patients enrolled, treated, and completing each study period) will be tabulated by cohort (and pooled cohorts) by treatment randomized (omalizumab or placebo) in the previous study in all patients with data. Premature study drug discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized. Eligibility criteria deviations and other major protocol deviations will be summarized.

6.5 EFFICACY ANALYSES

All efficacy analyses for this study will be presented by cohort and by treatment group (four groups: [1] Cohort A omalizumab, [2] Cohort A placebo, [3] Cohort B omalizumab, [4] Cohort B placebo). In addition, if no meaningful differences exist between cohorts with respect to the comparisons outlined in Section 6.3, and if efficacy results from Studies GA39688 and GA39855 appear consistent, the cohorts will be pooled for all efficacy analyses (two groups: [1] Cohorts A and B omalizumab, [2] Cohorts A and B placebo) in addition to being presented separately.

In all efficacy analyses, baseline will be defined as the last measurement from previous studies taken prior to randomization (i.e., baseline of Study GA39688 or GA39855). This definition of baseline is deemed the most meaningful because it allows for comparison of treatment regimens (i.e., 52 weeks of omalizumab treatment vs. 24 weeks of placebo followed by 28 weeks of omalizumab treatment). It also allows for a graphical assessment of the trajectory of the endpoint over the entire course of a 52-week treatment period (over the course of the current and previous studies) in both treatment groups. Assuming that omalizumab is beneficial as compared to placebo, it is expected that the distribution of continuous endpoints (e.g., NCS, NPS, etc.) at Week 24 (the beginning of this study) will meaningfully differ between the omalizumab and placebo groups. Therefore, it would be inappropriate to define baseline as the measurement taken at Week 24.

6.5.1 Efficacy Analysis Populations

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.

6.5.2 Primary Efficacy Endpoints

Because the primary analysis is descriptive in nature, there will be no formal hypothesis testing in the analysis of the primary efficacy endpoints.

6.5.2.1 Nasal Polyp Score

Polyp size in each nasal opening will be graded through an assessment of the video nasal endoscopy (0–4 integer scale, see Appendix 3; Gevaert et al. 2013) by a central panel of independent sinus surgeons who are blinded to treatment assignment in the previous 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). In addition to all timepoints through Week 24 of the previous study, in this OLE study NPS will be assessed on Weeks 36, 52, 64, and 76. Baseline NPS is defined as the last measurement from the previous study performed before randomization (i.e., baseline of Study GA39688/GA39855). The absolute change from baseline NPS values will be defined as the NPS at the timepoint minus the NPS at baseline.

Change from baseline of Study GA39688/GA39855 in NPS will be summarized at each timepoint by descriptive statistics on observed data (i.e., mean, median, standard deviation, and 95% CIs) by treatment group from Study GA39688/GA39855. Both efficacy and durability of response will be assessed descriptively and graphically, within patients enrolled in the OLE and randomized to omalizumab in Study GA39688/GA39855, according to the mean estimates of absolute change from baseline in NPS over all timepoints through Week 76, including data from timepoints from the previous studies.

In addition, the durability of response will be assessed, by treatment group from Study GA39688/GA39855, by descriptive analysis of the change from baseline at Weeks 52, 64, and 76 in NPS. The duration of response will be assessed in each arm separately as the last timepoint at which a meaningful change from baseline in NPS is present.

6.5.2.2 Nasal Congestion Score

NCS will be scored by patients as not at all, mild, moderate, or severe (a score of 0, 1, 2, or 3, respectively; see Appendix 4; Fairley et al. 1993) every morning through Week 76 via eDiary. Details on the calculation of the average daily NCS (i.e., number of days included) at baseline and at each timepoint will be provided in the SAP. In addition to monthly timepoints through Week 24 of the previous studies (from patients enrolled in the OLE), for each patient and monthly study timepoint of the OLE study (i.e., Weeks 52, 56, 60, 64, 68, 72, and 76), the NCS for that study visit will be defined as the average of the daily scores leading up to that timepoint. The absolute change from baseline in the average daily NCS values will be defined as the average NCS at the timepoint minus the average daily NCS at baseline, where baseline is defined as the average of the daily NCS over the period leading up to randomization. Through ongoing monitoring of eDiary compliance, investigators will aim to obtain at least 4 of the 7 days of data for NCS in any given week.

Change from baseline of Study GA39688/GA39855 at each timepoint in NCS will be summarized by descriptive statistics on observed data (i.e., mean, median, standard deviation, and 95% CIs) by treatment group from Study GA39688/GA39855. Both efficacy and durability of response will be assessed descriptively and graphically, within patients randomized to omalizumab in Study GA39688/GA39855, according to the mean estimates of absolute change from baseline in NCS over all timepoints through Week 76, including data from timepoints from the previous studies.

In addition, the durability of response will be assessed, by treatment group from Study GA39688/GA39855, by descriptive analysis of the change from baseline at Weeks 52, 56, 60, 64, 68, 72, and 76 in NCS. The duration of response will be assessed in each arm separately as the last timepoint at which a meaningful change from baseline in NCS is present.

6.5.3 Secondary Efficacy Endpoints

6.5.3.1 Nasal Polyp Score and Nasal Congestion Score

The impact of longer treatment duration on durability of response according to NPS and NCS will be assessed separately using two mixed-effect model repeated measurement (MMRM) models for NPS and NCS as dependent variables, respectively. The models will use absolute change from baseline of Study GA39688/GA39855 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 (at a minimum the model will include Weeks 24, 36, 52, 64, and 76), Study GA39688/GA39855 baseline NPS (or NCS, respectively), treatment, treatment by timepoint interaction, and Study GA39688/GA39855 baseline NPS (or NCS, respectively) by timepoint interaction. Further details about the model and additional covariates will be described in the SAP. Point estimates, 95% CIs, and p-values for the treatment effect (omalizumab vs. placebo) on absolute change from Study GA39688/GA39855 baseline in NPS (or NCS, respectively) will be calculated on the basis of the model for all modeled timepoints, including Week 76, using appropriate contrasts.

The SAP will describe adjustments, if any, for potential unspecified confounders of treatment group differences due to the fact that enrollment into the OLE occurs post-randomization into the previous studies.

6.5.3.2 Nasal Symptoms

Nasal symptoms other than NCS (i.e., TNSS, loss of smell, posterior rhinorrhea, and anterior rhinorrhea) will be analyzed according to the same methods as those used for NCS score specified in Section 6.5.2.2 and using separate MMRM models as specified above.

6.5.3.3 SNOT-22, UPSIT, EQ-5D-5L, and AQLQ

SNOT-22, UPSIT, EQ-5D-5L, and AQLQ will be analyzed according to the same methods as those used for NPS as specified in Section 6.5.2.1 and using separate MMRM models as specified above.

6.5.4 Exploratory Efficacy/Psychometric Endpoints

For the for MOS Sleep Scale and Healthy Days Core Module, change from Week 24 to Weeks 36, 52, 64, and 76 will be summarized by descriptive statistics on observed data (i.e., mean, median, standard deviation, and 95% CIs) by treatment randomized to (placebo/omalizumab) from the previous studies. Further details on the analysis of reduction in need for surgery, requirement of rescue treatment, having had surgery for nasal polyps, MOS Sleep Scale, Healthy Days Core Module, as well as the PGIC will be described in the SAP.

6.6 SAFETY ANALYSES

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 grouped according to the treatment assigned (omalizumab or placebo) at randomization of the previous studies.

Safety will be assessed through the summary of exposure to study drug, adverse events, and laboratory test results.

Exposure to omalizumab (number of omalizumab administrations and duration of treatment) will be summarized for the OLE by treatment group assigned (omalizumab or placebo) at randomization of the previous studies.

6.6.1 Primary Safety Analysis: Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be coded and their incidence will be summarized. A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug. Only adverse events that occurred during the OLE will be summarized. In addition, separate summaries will be generated for serious adverse events, deaths, adverse events of special interest as defined in Section 5.2.3, and adverse events leading to discontinuation of study drug.

6.6.2 Secondary Safety Analysis: Clinical Laboratory Evaluations

Descriptive summaries of laboratory values at Study GA39688/GA39855 baseline and throughout the study will be generated for selected parameters. For these selected parameters, changes from baseline and the proportion of patients experiencing clinically significant changes relative to baseline will be compared between treatment groups as randomized in the previous studies.

6.7 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Predose serum omalizumab concentrations (C_{min}) and total and free IgE will be measured at Week 36 and Week 52 during the treatment period and at Weeks 64 and 76 during the follow-up period according to the summary of activities (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.

Additional PK analyses will be conducted as appropriate.

6.8 INTERIM ANALYSIS

The Sponsor may choose to conduct one interim analysis depending on the results of Study GA39688 or GA39855 (e.g., if time to maximum efficacy has not plateaued by Week 24). Results from this interim analysis may be used to support a marketing application with health authorities based on results from the previous Study GA39688/GA39855. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel, who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures. Any optional interim analysis will be performed after database lock of the previous studies (Studies GA39688/GA39855). In this situation, investigators will remain blinded to individual treatment assignment from the previous studies (Studies GA39688/GA39855).

6.9 MISSING DATA

Unless otherwise noted, in the analysis of all continuous co-primary, secondary, and exploratory endpoints, missing values will not be explicitly imputed in the analyses, which will be based on descriptive statistics for the co-primary efficacy endpoints and on mixed-effect model repeated measurement (MMRM) models for the secondary efficacy endpoints. Patients without post-baseline efficacy endpoint data will not contribute to the MMRM models.

6.10 UNUSED AND SPURIOUS DATA

For the efficacy analysis of continuous co-primary, secondary, and exploratory endpoints, a single data point will be assigned to a planned timepoint (e.g., Weeks 4, 8, 16, 24, 36, 52, 64, and 76) according to the Schedule of Activities for that particular endpoint (see Appendix 1) based on the proximity of the date of the assessment to the planned timepoint and may include data collected as part of a planned, unscheduled, safety follow-up, dosing termination, or early termination visit. All data points collected but not assigned to a planned timepoint in the analysis will be unused in the planned

analysis. Further details on the assignment of data points to planned timepoints for analysis will be described in the SAP.

Due to the nature of the data capture instruments (e.g., eCRF, eDiary, or tablet), spurious response data is not expected for PRO efficacy endpoints. In the event of a documented device malfunction leading to spurious data (i.e., a date that is recorded prior to the date of first patient screened or after last patient's last visit), those data will be ignored (assumed missing) for the purpose of efficacy analysis and discussed in the Clinical Study Report (CSR). Any spurious lab values or vital sign measurements will be excluded from summary tables and discussed in the CSR.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory, central imaging, eDiary/ePRO, and IWRS data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Some PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

Some data from patient assessments will be collected on paper and entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME

Patients will use an electronic device to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union

or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will

be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

Omalizumab in the treatment of nasal polyposis is a joint development project between F. Hoffmann-La Roche Ltd and Novartis Pharmaceuticals. This study is sponsored by F. Hoffmann-La Roche Ltd and will be managed by F. Hoffmann-La Roche Ltd and a contract research organization (CRO). The CRO will manage clinical site operations and medical monitoring.

Approximately 100–140 sites globally are expected to participate. It is anticipated that a maximum of approximately 240 patients will enroll in this study, as per Section 6.1. An IWRS will be used for study drug inventory management and to randomize patients to study drug.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests and PK and ADA analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Samples for urine pregnancy tests will be analyzed at the local laboratory. Samples for PD, PK, and antibody tests will be sent to the Sponsor or a designee for analysis. All other samples will be sent to one of several central laboratories for analysis.

PRO data will be recorded electronically via devices supplied by a PRO vendor. Patients will be provided an eDiary device for answering questions on controller medication and rescue use.

Endoscopy reads will be read centrally and managed by a central reading vendor.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

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

Appendix 1
Schedule of Activities (cont.)

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

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.

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

[b] Patients who discontinue study drug or discontinue from the study will be asked to complete the DT/ET visit.

[c] 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.

[d] 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.

[e] 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.

[f] 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.

[g] 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 1
Schedule of Activities (cont.)

[h] AQLQ only in asthma patients

[i] The Week 36 PK, total IgE, and free IgE collection should be conducted prior to the omalizumab dose.

[j] 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.

[k] Vital signs collected at every visit (every 2 weeks in patients receiving omalizumab Q2W and every 4 weeks in patients receiving omalizumab Q4W).

[l] Adverse events and concomitant medications should be assessed and recorded at least monthly.

[m] Patients will remain on mometasone intranasally throughout the study as specified in Section 4.3.3. At each visit the investigator must ensure that the patient has the necessary doses up to the next visit.

Appendix 2
Omalizumab Dosing Table for Nasal Polyps

Baseline IgE (IU/mL) (Day -35)	Body Weight (kg) (Day -35)							
	>30-40	> 40–50	> 50–60	> 60–70	> 70–80	> 80–90	> 90–125	>125–150
≥ 30–100	75 mg Q4wk	150 mg Q4wk	150 mg Q4wk	150 mg Q4wk	150 mg Q4wk	150 mg Q4wk	300 mg Q4wk	300 mg Q4wk
> 100–200	150 mg Q4wk	300 mg Q4wk	300 mg Q4wk	300 mg Q4wk	300 mg Q4wk	300 mg Q4wk	450 mg Q4wk	600 mg Q4wk
> 200–300	225 mg Q4wk	300 mg Q4wk	300 mg Q4wk	450 mg Q4wk	450 mg Q4wk	450 mg Q4wk	600 mg Q4wk	375 mg Q2wk
> 300–400	300 mg Q4wk	450 mg Q4wk	450 mg Q4wk	450 mg Q4wk	600 mg Q4wk	600 mg Q4wk	450 mg Q2wk	525 mg Q2wk
> 400–500	450 mg Q4wk	450 mg Q4wk	600 mg Q4wk	600 mg Q4wk	375 mg Q2wk	375 mg Q2wk	525 mg Q2wk	600 mg Q2wk
> 500–600	450 mg Q4wk	600 mg Q4wk	600 mg Q4wk	375 mg Q2wk	450 mg Q2wk	450 mg Q2wk	600 mg Q2wk	
> 600–700	450 mg Q4wk	600 mg Q4wk	375 mg Q2wk	450 mg Q2wk	450 mg Q2wk	525 mg Q2wk		
> 700–800	300 mg Q2wk	375 mg Q2wk	450 mg Q2wk	450 mg Q2wk	525 mg Q2wk	600 mg Q2wk		
> 800–900	300 mg Q2wk	375 mg Q2wk	450 mg Q2wk	525 mg Q2wk	600 mg Q2wk			
> 900–1000	375 mg Q2wk	450 mg Q2wk	525 mg Q2wk	600 mg Q2wk				
> 1000–1100	375 mg Q2wk	450 mg Q2wk	600 mg Q2wk		DO NOT ADMINISTER			
> 1100–1200	450 mg Q2wk	525 mg Q2wk	600 mg Q2wk					
> 1200–1300	450 mg Q2wk	525 mg Q2wk						
> 1300–1500	525 mg Q2wk	600 mg Q2wk						

Q2wk = once every 2 weeks; Q4wk = once every 4 weeks.

Lighter gray shading with **black text** indicates doses to be administered by subcutaneous injection **every 4 weeks**.

Darker gray shading with **white text** indicates doses to be administered by subcutaneous injection **every two weeks**.

Source: E.U. Xolair Summary of Product Characteristics, October 2016.

Appendix 3
Nasal Polyps Scoring System

Polyp Score	Polyp Size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate [a]
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity

Notes: Scoring system is used to evaluate polyp size in each nasal passage by means of video nasal endoscopy. Nasal polyp score is the sum of unilateral polyp scores for each nasal passage.

[a] The scoring is modified to accommodate patients who have had a middle turbinectomy, such that the polyp must reach the top of the inferior turbinate to be graded as Score 2.

Source: Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol 2013;131:110–6.e1.

Appendix 4
Nasal Symptoms Assessed Daily via Electronic Diary

1. Is your nose blocked? [a]

   0 = Not at all 1 = Mild 2 = Moderate 3 = Severe

2. Is your sense of smell reduced?

   0 = Not at all 1 = Mild 2 = Moderate 3 = Severe

3. Do you have a runny nose?

   0 = Not at all 1 = Mild 2 = Moderate 3 = Severe

4. Do you feel dripping at the back of the nose?

   0 = Not at all 1 = Mild 2 = Moderate 3 = Severe

[a] The Nasal Congestion Score (NCS) will be assessed with Question 1 only.

NOTE: This is an example of the content; formatting may be adjusted for adaptation to the tablet electronic patient-reported outcome device.

Appendix 5
Nasal Symptoms Assessed via In-Clinic or Telephone Interview

1. Over the past week, was your nose blocked?

   0 = Not at all 1 = Mild 2 = Moderate3 = Severe

2. Over the past week, was your sense of smell reduced?

   0 = Not at all 1 = Mild 2 = Moderate3 = Severe

3. Over the past week, did you have a runny nose?

   0 = Not at all 1 = Mild 2 = Moderate3 = Severe

4. Over the past week, did you feel dripping at the back of the nose?

   0 = Not at all 1 = Mild 2 = Moderate3 = Severe

Note: These nasal symptoms will be assessed in-clinic or via telephone interview, as per schedule of activities in Appendix 1. Study staff will read questions and all responses aloud verbatim, and patients will respond verbally. Subject answers will be recorded in the electronic data capture system.

Appendix 6
Sino-Nasal Outcome Test-22 (SNOT-22) Questionnaire

Below you will find a list of symptoms and social/emotional consequences of your nasal disorder. We would like to know more about these problems and would appreciate you answering the following question to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems, as they have been over the past 2 weeks. Thank you for your participation.

Considering how severe the problem is when you experience it and how frequently it happens, please rate each item below on how "bad" it is by circling the number that corresponds with	**No problem**	**Very mild problem**	**Mild or slight problem**	**Moderate problem**	**Severe problem**	**Problem as bad as it can be**
1. Need to blow nose	0	1	2	3	4	5
2. Sneezing	0	1	2	3	4	5
3. Runny nose	0	1	2	3	4	5
4. Cough	0	1	2	3	4	5
5. Post nasal discharge (dripping at he back of your nose)	0	1	2	3	4	5
6. Thick nasal discharge	0	1	2	3	4	5
7. Ear fullness	0	1	2	3	4	5
8. Dizziness	0	1	2	3	4	5
9. Ear pain	0	1	2	3	4	5
10. Facial pain/pressure	0	1	2	3	4	5
11. Difficulty falling asleep	0	1	2	3	4	5
12. Waking up at night	0	1	2	3	4	5
13. Lack of a good night's sleep	0	1	2	3	4	5
14. Waking up tired	0	1	2	3	4	5
15. Fatigue	0	1	2	3	4	5
16. Reduced productivity	0	1	2	3	4	5
17. Reduced concentration	0	1	2	3	4	5
18.Frustrated/restless/irritable	0	1	2	3	4	5
19. Sad	0	1	2	3	4	5
20. Embarrassed	0	1	2	3	4	5
21. Sense of taste/smell	0	1	2	3	4	5
22. Blockage/congestion of nose	0	1	2	3	4	5

NOTE: This is an example of the content; formatting may be adjusted for adaptation to the tablet electronic patient-reported outcome device.

Appendix 7
Patient Global Impression of Change

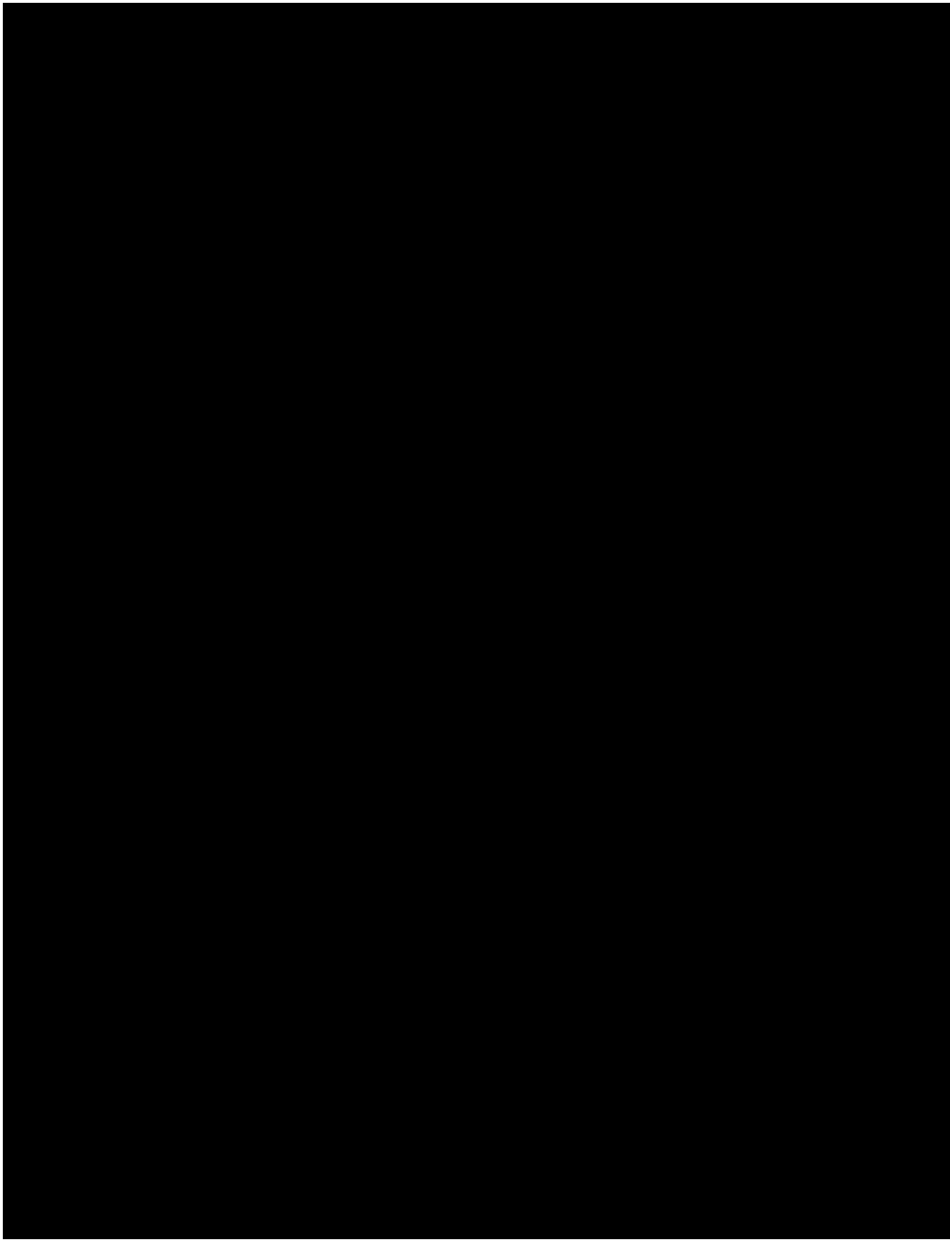
Please choose one of the following options that best describes the change in the severity of your nasal polyps symptoms since your previous study visit: (Check one response)

- ☐ Very much better
- ☐ Much better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Much worse
- ☐ Very much worse

NOTE: This is an example of the content; formatting may be adjusted for adaptation to the tablet electronic patient-reported outcome device.

Appendix 8 Asthma Quality of Life Questionnaire

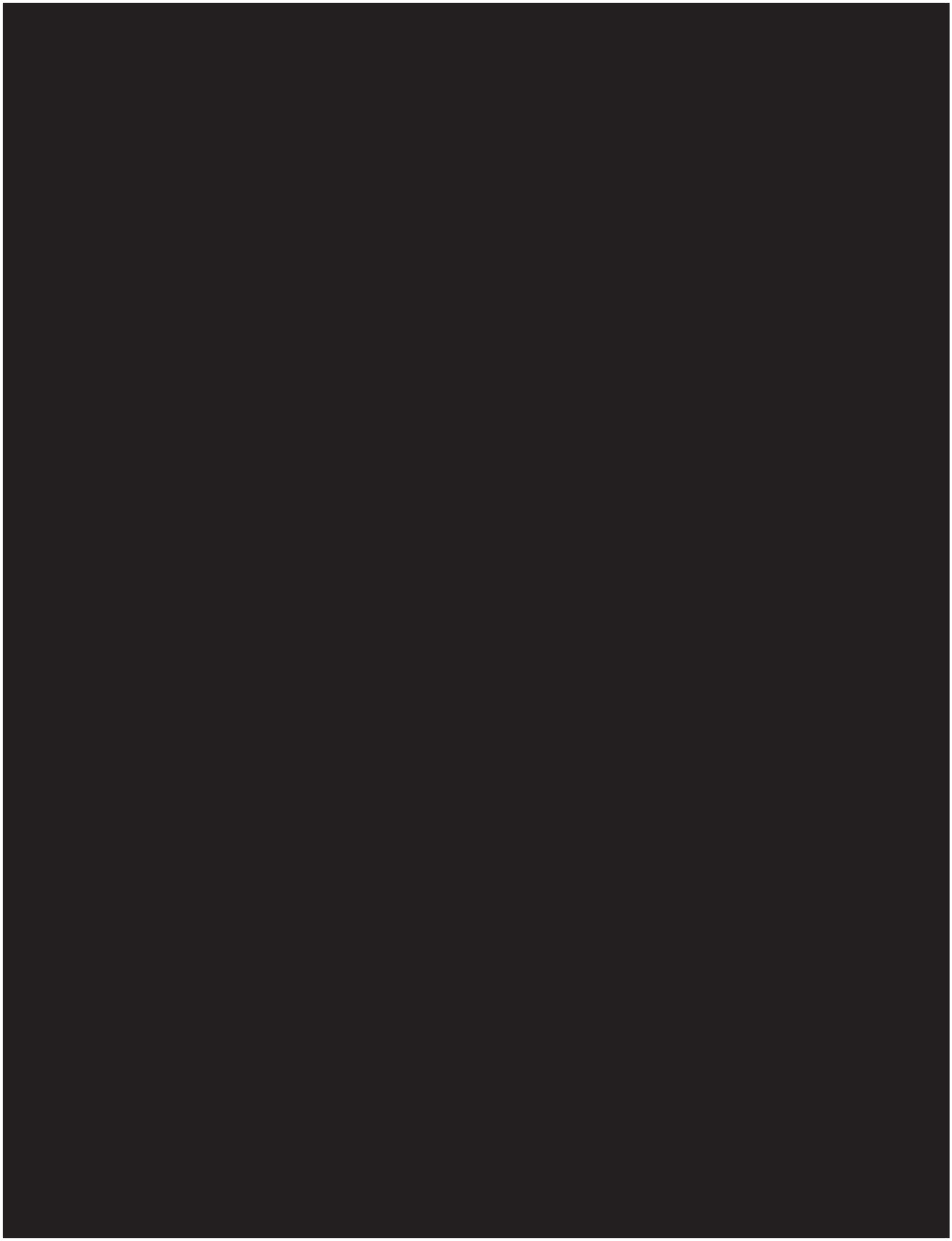
[redacted]



[redacted]

[redacted]

[redacted]



Appendix 9 EuroQol 5-Dimension 5-Level Questionnaire

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking. ❑
I have slight problems walking. ❑
I have moderate problems walking. ❑
I have severe problems walking. ❑
I am unable to walk. ❑

SELF-CARE

I have no problems washing or dressing myself. ❑
I have slight problems washing or dressing myself. ❑
I have moderate problems washing or dressing myself. ❑
I have severe problems washing or dressing myself. ❑
I am unable to wash or dress myself. ❑

USUAL ACTIVITIES *(e.g., work, study, housework, family or leisure activities)*

I have no problems doing my usual activities. ❑
I have slight problems doing my usual activities. ❑
I have moderate problems doing my usual activities. ❑
I have severe problems doing my usual activities. ❑
I am unable to do my usual activities. ❑

PAIN/DISCOMFORT

I have no pain or discomfort. ❑
I have slight pain or discomfort. ❑
I have moderate pain or discomfort. ❑
I have severe pain or discomfort. ❑
I have extreme pain or discomfort. ❑

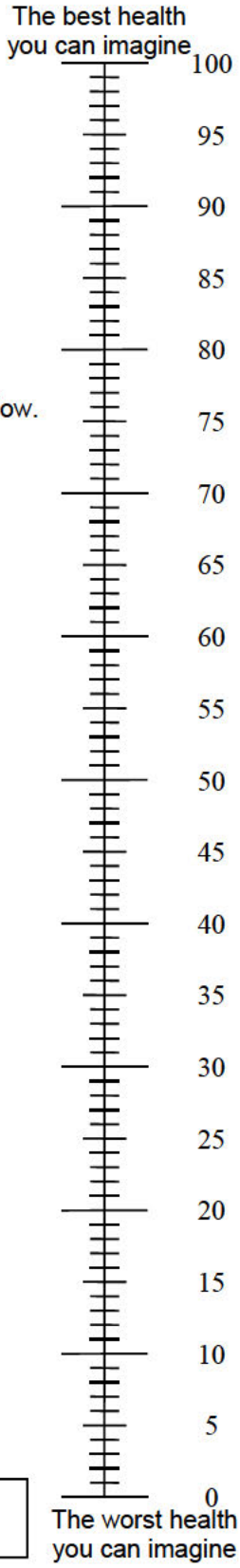
ANXIETY/DEPRESSION

I am not anxious or depressed. ❑
I am slightly anxious or depressed. ❑
I am moderately anxious or depressed. ❑
I am severely anxious or depressed. ❑
I am extremely anxious or depressed. ❑

Appendix 9 EuroQol 5-Dimension 5-Level Questionnaire (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



NOTE: This is an example of the content; formatting may be adjusted for adaptation to the tablet electronic patient-reported outcome device.

Appendix 10
Medical Outcomes Study Sleep Scale

Sleep Scale from the Medical Outcomes Study

1. How long did it usually take for you to fall asleep during the past 4 weeks?

(Circle One)

0-15 minutes……..…1

16-30 minutes……..2

31-45 minutes……..3

46-60 minutes……..4

More than 60 minutes …….5

---

2. On the average, how many hours did you sleep each night during the past 4 weeks?

Write in number
of hours per night: ☐☐

Appendix 10
Medical Outcomes Study Sleep Scale (cont.)

How often during the past 4 weeks did you…

	(Circle One Number On Each Line)					
	All of the Time ▼	Most of the Time ▼	A Good Bit of the Time ▼	Some of the Time ▼	A Little of the Time ▼	None of the Time ▼
3. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	1	2	3	4	5	6
4. get enough sleep to feel rested upon waking in the morning?	1	2	3	4	5	6
5. awaken short of breath or with a headache?	1	2	3	4	5	6
6. feel drowsy or sleepy during the day?	1	2	3	4	5	6
7. have trouble falling asleep?	1	2	3	4	5	6
8. awaken during your sleep time and have trouble falling asleep again?	1	2	3	4	5	6
9. have trouble staying awake during the day?	1	2	3	4	5	6
10. snore during your sleep?	1	2	3	4	5	6
11. take naps (5 minutes or longer) during the day?	1	2	3	4	5	6
12. get the amount of sleep you needed?	1	2	3	4	5	6

Hays, R. D., & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), Measuring functioning and well-being: The Medical Outcomes Study approach (pp. 235-259), Durham, NC: Duke University Press.

NOTE: This is an example of the content; formatting may be adjusted for adaptation to the tablet electronic patient-reported outcome device.

Appendix 11
Healthy Days Core Module

1. Would you say that in general your health is: (Circle one)

excellent very good good fair poor

2. Now thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?

☐ days

3. Now thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?

☐ days

4. During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation?

☐ days

NOTE: This is an example of the content; formatting may be adjusted for adaptation to the tablet electronic patient-reported outcome device.

Appendix 12
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.